THE HARVEY SOCIETY

THE HARVEY LECTURES

DELIVERED UNDER THE AUSPICES OF

THE HARVEY SOCIETY OF NEW YORK

1907-08

BY

PROF. EDWIN O. JORDAN
PROF. JAMES EWING
PROF. DAVID L. EDSALL
PROF. ERNEST H. STARLING
PROF. GEORGE CRILE
PROF. JOSEPH JASTROW
PROF. OTTO FOLIN
PROF. ROSS G. HARRISON
PROF. E. A. SCHÄFER
PROF. ALONZO E. TAYLOR

PHILADELPHIA AND LONDON
J. B. LIPPINCOTT COMPANY
1909

OFFICERS AND MEMBERS OF THE SOCIETY

OFFICERS

Graham Lusk, *President*
James Ewing, *Vice-President*
Edward K. Dunham, *Treasurer*
George B. Wallace, *Secretary*

COUNCIL

Simon Flexner
Theodore Janeway
Philip Hanson Hiss
The Officers Ex-Officio

ACTIVE MEMBERS

Dr. John Auer
Dr. S. P. Beebe
Dr. Hermann M. Biggs
Dr. Harlow Brooks
Dr. R. Burton-Opitz
Dr. John G. Curtis
Dr. Edward K. Dunham
Dr. Haven Emerson
Dr. James Ewing
Dr. Simon Flexner
Dr. Austin Flint
Dr. William J. Gies
Dr. R. A. Hatcher
Dr. C. A. Herter
Dr. Philip Hanson Hiss
Dr. Eugene Hodenpyl
Dr. Holmes C. Jackson
Dr. Theodore C. Janeway
Dr. Frederic S. Lee
Dr. P. A. Levene
Dr. E. Libman
Dr. Graham Lusk
Dr. John A. Mandel
Dr. S. J. Meltzer
Dr. Adolf Meyer
Dr. Hideyo Noguchi
Dr. Charles Norris
Dr. Horst Oertel
Dr. Eugene L. Opie
Dr. William H. Park
Dr. T. Mitchell Prudden
Dr. A. N. Richards
Dr. A. J. Wakeman
Dr. George B. Wallace
Dr. Robert J. Wilson
Dr. C. G. L. Wolf
Dr. Francis Carter Wood

ASSOCIATE MEMBERS

Dr. Charles F. Adams
Dr. Isaac Adler
Dr. Samuel Alexander
Dr. S. T. Armstrong
Dr. Pearce Bailey
Dr. L. Bolton Bangs
Dr. Joseph A. Blake
Dr. David Bovaird
Dr. John W. Brannan
Dr. Nathan E. Brill
Dr. Edward B. Bronson
Dr. F. Tilden Brown
Dr. S. A. Brown
Dr. Joseph D. Bryant
Dr. Glenworth R. Butler
Dr. C. N. B. Camac
Dr. Robert J. Carlisle
Dr. John H. Claiborne
Dr. Warren Coleman
Dr. William B. Coley
Dr. Joseph Collins
Dr. Lewis A. Conner
Dr. Floyd M. Crandall
Dr. B. Farquhar Curtis
Dr. Charles L. Dana
Dr. Thomas Darlington
Dr. D. Bryson Delaven
Dr. Edward B. Dench
Dr. W. K. Draper
Dr. Alexander Duane
Dr. Theodore Dunham
Dr. Max Einhorn
Dr. George T. Elliot
Dr. Charles A. Elsberg
Dr. Evan M. Evans
Dr. Edward D. Fisher
Dr. John A. Fordyce
Dr. Joseph Fraenkel
Dr. Wolff Freudenthal
Dr. Arpad G. Gerster
Dr. Virgil P. Gibney
Dr. Charles L. Gibson
Dr. J. Riddle Goffe
Dr. Frederick Gwyer
Dr. A. McL. Hamilton
Dr. Graeme M. Hammond
Dr. T. Stuart Hart
Dr. Frank Hartley
Dr. John A. Hartwell
Dr. Thomas W. Hastings
Dr. Henry Heiman
Dr. Augustus Hoch
Dr. L. Emmett Holt
Dr. John Howland
Dr. John H. Huddleston
Dr. George S. Huntington
Dr. Abraham Jacobi
Dr. George W. Jacoby
Dr. Walter B. James
Dr. Edward G. Janeway
Dr. Frederic Kammerer
Dr. Jacob Kauffmann
Dr. Charles G. Kerley
Dr. Philip D. Kerrison
Dr. Eleanor B. Kilham
Dr. Francis P. Kinnicutt
Dr. Arnold Knapp
Dr. Herman Knapp
Dr. L. E. La Fetra
Dr. Alexander Lambert
Dr. Samuel W. Lambert
Dr. Gustav Langmann
Dr. Egbert Le Fevre
Dr. Isaac Levin
Dr. Charles H. Lewis
Dr. Robert Lewis, Jr.
Dr. William C. Lusk
Dr. Sigmund Lustgarten
Dr. David H. McAlpin
Dr. Charles McBurney
Dr. Arthur R. Mandel
Dr. Morris Manges

ASSOCIATE MEMBERS—*Continued*

Dr. George Mannheimer
Dr. Wilbur B. Marple
Dr. Frank S. Meara
Dr. Victor Meltzer
Dr. Walter Mendelson
Dr. Alfred Meyer
Dr. Willy Meyer
Dr. Michael Michailovsky
Dr. John P. Munn
Dr. Van Horne Norrie
Dr. Henry S. Patterson
Dr. George L. Peabody
Dr. Frederick Peterson
Dr. William M. Polk
Dr. Sigismund Pollitzer
Dr. Nathaniel B. Potter
Dr. William B. Pritchard
Dr. William J. Pulley
Dr. Francis J. Quinlan
Dr. Edward Quintard
Dr. Charles C. Ransom
Dr. Andrew R. Robinson
Dr. Julius Rudisch
Dr. Bernard Sachs
Dr. Thomas E. Satterthwaite
Dr. Reginald H. Sayre
Dr. Max G. Schlapp
Dr. Otto H. Schultze
Dr. Fritz Schwyzer
Dr. Newton M. Shaffer
Dr. William K. Simpson
Dr. A. Alexander Smith
Dr. M. Allen Starr
Dr. George D. Stewart
Dr. Lewis A. Stimson
Dr. William S. Stone
Dr. Parker Syms
Dr. John S. Thacher
Dr. W. Gilman Thompson
Dr. William H. Thomson
Dr. Richard Van Santvoord
Dr. John B. Walker
Dr. Josephine Walter
Dr. John E. Weeks
Dr. Frederick H. Wiggin
Dr. Herbert B. Wilcox
Dr. W. R. Williams
Dr. Margaret B. Wilson
Dr. John Van Doren Young
Dr. Hans Zinsser

HONORARY MEMBERS

Prof. J. G. Adami
Prof. Lewellys F. Barker
Prof. F. G. Benedict
Prof. W. T. Councilman
Prof. G. W. Crile
Prof. D. L. Edsall
Prof. Otto Folin
Prof. Ross G. Harrison
Prof. W. H. Howell
Prof. Joseph Jastrow
Prof. E. O. Jordan
Prof. Lafayette B. Mendel
Prof. Hans Meyer
Prof. Charles S. Minot
Prof. T. H. Morgan
Prof. Friedrich Müller
Prof. Carl von Noorden
Prof. Frederick G. Novy
Prof. W. T. Porter
Prof. E. A. Schäfer
Prof. Theobald Smith
Prof. E. H. Starling
Prof. A. E. Taylor
Prof. J. Clarence Webster
Prof. E. B. Wilson
Sir Almroth Wright

PREFACE

WITH the appearance of this third volume of the Lectures of the Harvey Society it would seem that the hope of the founders of the Society that the lectures should play an important part in the diffusion of our knowledge of scientific medicine had been realized. It is believed that the lectures maintain the high standard set by the two preceding volumes, and that the scientific world is beginning to evince a lively interest in the possibility of obtaining in concise form the authoritative views of specialists in a large number of medical and biological subjects upon their own particular field of research. It is a pleasure to announce that the fourth volume will shortly appear.

The thanks of the Council of the Society are due to the Editors of the *Journal of the American Medical Association* and the *Archives of Internal Medicine* for the use of plates for illustration and for permission to reprint lectures which were published in those journals, to the Editors of the *Boston Medical and Surgical Journal* and of the *Anatomical Record* for the use of plates and for permission to reprint, and, lastly, to the Royal Society of Edinburgh for the use of plates to illustrate Dr. Schäfer's lecture.

CONTENTS

LIST OF ILLUSTRATIONS

THE PROBLEMS OF SANITATION*

EDWIN O. JORDAN, Ph.D.,
Professor of Bacteriology, University of Chicago.

TWENTY-FIVE years ago Mr. Frederic Harrison, writing of the nineteenth century, gave us this picture of London, the largest city of the modern world, and, indeed, of all time.

"To bury Middlesex and Surrey under miles of flimsy houses, crowd into them millions and millions of over-worked, under-fed, half-taught, and often squalid men and women; to turn the silver Thames into the biggest sewer recorded in history; to leave us all to drink the sewerage water, to breathe the carbonized air, to be closed up in a labyrinth of dull, sooty, unwholesome streets; to leave hundreds and thousands confined there, with gin, and bad air, and hard work, and low wages, breeding contagious diseases, and sinking into despair of soul and feebler conditions of body; and then to sing pæans and shout, because the ground shakes and the air is shrill with the roar of infinite engines and machines, because the blank streets are lit up with garish gas-lamps, and more garish electric lamps, and the postoffice carries billions of letters, and the railways every day carry 100,000 persons in and out of the huge factory we call the greatest metropolis of the civilized world—this is surely not the last word in civilization."

We need not pause now to inquire whether this characterization of the London of the nineteenth century was correct, or, admitting that it was, whether it is now true of London or any other city, whether the human race at the beginning of the twentieth century is still dazzled and bewildered by its sudden material acquisitions, whether we are even now rushing violently down a steep place into sea; I would simply ask you to remark the large part that faults and defects of sanitation play in Mr. Harrison's eloquent indictment. Some of the hardest things said about the nineteenth century by its critics refer to the neglect of public hygiene. Again and again the luxury

* Lecture delivered October 26, 1907.

of a few and the comfort of more are contrasted with the unhygienic conditions under which many others are forced to live and work. Unhygienic conditions in themselves are nothing new. In mediæval London, and indeed throughout Europe, the dwelling places and mode of living of the majority of the citizens were far more unwholesome, far more conducive to the spread of infectious disease than in the London of 1882 or 1907. Mr. Harrison himself in another connection thus pictures the life of the Middle Ages:

"The old Greek and Roman religion of external cleanness was turned into a sin. The outward and visible sign of sanctity now was to be unclean. No one was clean, but the devout Christian was unutterably foul. The tone of the Middle Ages in the matter of dirt was a form of mental disease. Cooped up in castles and walled cities, with narrow courts and sunless alleys, they would pass day and night in the same clothes, within the same airless, gloomy, windowless, and pestiferous chambers; they would go to bed without night-clothes and sleep under uncleansed sheepskins and frieze rugs; they would wear the same leather, fur, and woolen garments for a lifetime, and even for successive generations; they ate their meals without forks, and covered up the orts with rushes; they flung their refuse out of the window into the street or piled it up in the back yard; the streets were narrow, unpaved, crooked lanes through which, under the very palace turrets, men and beasts tramped knee-deep in noisome mire. This was at intervals varied with fetid rivulets and open cesspools; every church was crammed with rotting corpses and surrounded with graveyards, sodden with cadaveric liquids, and strewn with disinterred bones. Round these charnel houses and pestiferous churches were piled old decaying wooden houses, their sole air being these deadly exhalations, and their sole water-supply being these polluted streams or wells dug in this reeking soil. Even in the palaces and castles of the rich the same bestial habits prevailed. Prisoners rotted in noisome dungeons under the banqueting hall; corpses were buried under the floor of the private chapel; scores of soldiers and attendants slept in gangs for months together in the same hall or guardroom, where they ate and drank, played and fought."

At all events the city slum is not a modern institution. The main difference between the mediæval and the modern attitude towards unhygienic conditions lies in our having now become awake to the sources of disease and death and to the knowledge that much disease is preventable. The public conscience to-day winces and rebels at the sight of evils once

regarded with indifference or helplessness. So long as mankind supposed that, in the language of Cruden's "Concordance," "diseases and death are the consequences and effects of sin," so long did a bewildered resignation accompany the mysterious visitations of Providence. For many this was radically and permanently changed when the germ theory gave to the human race for the first time in its history a rational theory of disease susceptible of experimental verification. When the fact was established that much disease could be prevented, an enduring foundation was laid for works of sanitation.

The campaign against disease can be carried on in various ways. Individual cases of disease can be nursed with all the care that experience has shown to conduce to recovery, suitable drugs may be administered, surgical interference resorted to, individual peculiarities studied and taken advantage of; in fact, all the resources of modern medicine focused on the state of disturbance or abnormality in the individual patient. Such treatment has saved in the past, and will save in the future, many lives dear to friends and family and of incalculable value to country and race.

As a mass-method of attacking disease, however, it is distinctly palliative and not remedial. There is no man in his right mind who would not rather avoid disease altogether than be healed of a malady even by the most skilful physician. For many and evident reasons prevention must in the long run take precedence over cure.

Preventive measures fall conveniently into two classes—those dealing with the physical well-being and resistance of the individual, such as diet, muscular exercise, sleep, fatigue, the use of stimulants and narcotics, and the general efficiency of the bodily functions, and, secondly, those having special reference to environmental conditions or affecting many persons or communities. The methods that the individual may adopt to ward off disease and enhance resistance lie within the scope of personal hygiene, those that involve larger or smaller groups of individuals, constitute the province of public hygiene or sanitation.

THE RÔLE OF PERSONAL HYGIENE.

The methods for the furtherance of personal hygiene must be largely educative in character, and it must be recognized that the progress possible in this direction is distinctly limited by inherited constitutional factors. The prevention of disease and premature death is in many cases impossible even if the strictest and most efficacious regimen be maintained and if the hostile action of outside agencies be successfully avoided. In other words, some organisms carry within themselves the seeds of decay which germinate early and come to fruition in spite of all individual endeavors. A congenitally feeble or defective mechanism may be strengthened, but can not be remade. In most instances, however, measures of personal hygiene avail powerfully in promoting normal life and happiness and in some degree in preventing premature death. I need only mention the high resistance to many infectious diseases possessed by the well-nourished, properly exercised, undrugged individual. Improvement in personal hygiene must depend to a great extent on education, must necessarily be slow, and its success in preventing disease be conditioned in large part by the inherited constitution.

PUBLIC HYGIENE.

Any distinction between personal hygiene and public hygiene can not in the nature of things be an absolute one. The stream can not rise higher than its source, the welfare of the group is determined by that of the individuals composing it. More and more, too, the concerns of personal hygiene are tending to become problems of public hygiene. Bodily cleanliness is essentially a personal matter; it would be an absurdity in the present state of public opinion to legislate for compulsory bathing, and yet the establishment of free public baths is everywhere recognized as an important measure of public sanitation. The same thing applies to exercise and the establishment of municipal playgrounds and gymnasia. The principle is perfectly sound. Primarily the function of public hygiene is both to avert from the community as a whole the consequences of mis-

doing, neglect, or ignorance on the part of any one, or any number, of its members, and to provide for groups of individuals, conditions as favorable for health and happiness as the most intelligent and far-seeing could demand for themselves. Such conditions may not always be those that the least intelligent or most greedy members of the community desire, but from the point of view of public hygiene they are none the less inevitable.

Up to the present, measures of sanitation have affected chiefly the infectious diseases. This is shown, for example, by the list of the ten leading causes of death in Massachusetts in 1856 and in 1904 (Table I).

TABLE I.

THE TEN LEADING REPORTED CAUSES OF DEATH IN MASSACHUSETTS IN ORDER OF FREQUENCY.

1856.	1904.
Consumption.	Heart Disease.
Scarlet Fever.	Consumption.
Brain Disease.	Pneumonia.
Old Age.	Diseases of Brain and Cord.
Pneumonia.	Diseases of Kidneys.
Typhoid Fever.	Cancer.
Dysentery.	Cholera Infantum.
Heart Disease.	Accidents.
Cholera Infantum.	Bronchitis.
Diphtheria and Croup.	Diarrhœa and Cholera Morbus.

In 1904 typhoid fever had dropped to thirteenth, dysentery to seventeenth, and scarlet fever to twenty-first place.

It is here seen that the diseases that have been displaced are largely the infectious diseases. It is not possible in all cases to determine the factors that have been operative in the decline, and in some cases causes beyond our control have perhaps been at work, but undoubtedly measures of quarantine, isolation, school hygiene, and other protective devices adopted by the community have played a part in the shrinking of once prevalent infections. In some instances the effect of methods of sanitation is not to be mistaken. One of the most remarkable, as indeed one of the best understood examples of the efficacy of

sanitary features, is afforded in the influence of improved public water supply on typhoid fever.

The improvement that has followed the substitution of a pure water supply for a polluted one in cities like Lawrence and Albany is unmistakable.

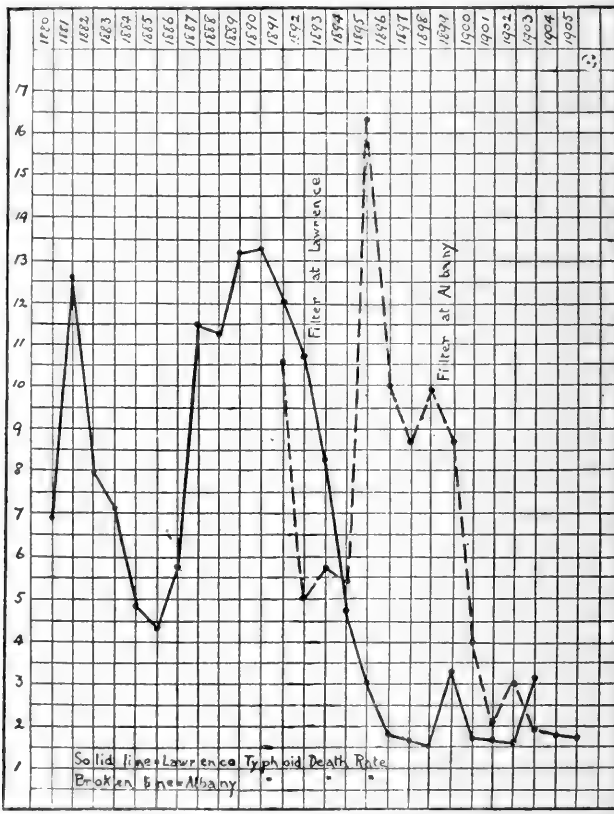


CHART 1.—Typhoid death rates in Albany, N. Y., and Lawrence, Mass., before and after installation of filters.

It is not my purpose, however, to rehearse the triumphs of sanitation. There is much to be accomplished before we can legitimately give ourselves the gratification of dwelling on past achievements. It seems to me desirable to keep before our

minds the present outlook for applying scientific knowledge to the prevention of disease rather than the historical development of, or even the recent advances in, sanitation. In many directions it is evident that we need further information before we can plan an intelligent campaign. As regards typhoid fever, for example, it is true that even after a pure public water supply has been secured the typhoid death rate remains

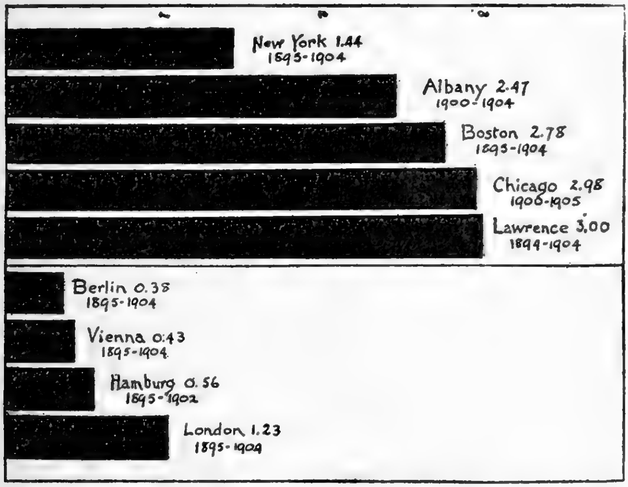


CHART 2.—Typhoid death rates in American and European cities—Albany, Lawrence and Hamburg—after installation of filters; Chicago after opening of the sanitary drainage canal. The remarkable case of the City of Washington, D. C., is purposely left out. There the installation of a modern sand filtration plant (November, 1905) was followed in the next year (1906) by a higher typhoid death rate (4.93) than had been recorded for either of the three preceding years (1903, 4.50; 1904, 4.38; 1905, 4.39).

excessively high in most American cities as compared with European cities somewhat similarly conditioned.

The relative proportions of this residual typhoid derived from direct contact, from milk, oysters, and other articles of food, from the agency of flies, from shallow wells[1] and other sources are not known. Owing to the great prevalence of typhoid fever in this country, cases contracted outside of pure-

[1] In 1899 from 3500 to 4000 such wells were in use in the city of St. Louis.

water districts are probably imported into them more frequently here than abroad. Typhoid bacillus carriers, like the cook discovered by Soper,[2] who was responsible for 32 cases of typhoid fever in seven families, are also, for the same reason, probably more numerous here than in Germany, but we have no precise information on these points.

INFANT MORTALITY.

Again, how much do we really know about the best methods of preventing summer mortality among infants in large cities? We have accumulated a considerable body of data about infant feeding, the advantages of fresh air and pure milk, but do we yet know to what extent our initial preventive measures have affected infant mortality or is there general agreement as to what the next step should be? Is there any likelihood that either "certified milk" or "pasteurized milk" will prove the final solution? Do we know in what proportion of cases domestic infection is the cause of infant diarrhœa, and whether such domestic infection in the tenement-house districts can be prevented in any other way than by the slow and wasteful process of individual education? Is there adequate provision for a statistical basis for determining the effect of such preventive measures as may be instituted? It is well known to statisticians that, unless the number of births is ascertained, deductions as to infant mortality cannot be well founded. In this country the record of births is in most places so defective that I may be pardoned perhaps for illustrating the errors into which we may fall in estimating infant mortality without knowledge of this factor.

TABLE II.

INFANT MORTALITY.

Population of about 150,000.	Deaths under 1 year.	Infant deaths per 10,000 population.	Total deaths.	Per cent. infant deaths of total deaths.	Births.	Infant deaths per 100 births; true infant death rate.
Town A....	650	43.3	2181	29.8	4555	14.2
Town B....	498	33.2	3780	13.2	2879	17.2

[2] Jour. Amer. Med. Assn., June 16, 1907, 2019.

In some cases, therefore, we are compelled to ask ourselves whether an apparent decline in infant mortality is due simply to a decline in birth rate or to a genuine amelioration in sanitary conditions. Since seasonal fluctuations and variations render short-time statistics of little value, it is evident that the answer to the question can hardly be an immediate one.

In England, it is stated, the infant mortality has not materially decreased during the last twenty-five years, although the general death rate has fallen considerably.[3] Newman, in his recent book on infant mortality, regards it as demonstrated that the infant mortality rate is not declining, and bases far-reaching conclusions on this assumption. Germany, however, shows a steadily lowering mortality rate since 1885, the quinquennial averages for the large towns showing successive diminution.[4] In the United States the available data are very meagre owing to the incomplete record of births. According to the records, however, the infant mortality in Boston and New York has steadily fallen by quinquennial periods since 1886.

TABLE III.

DEATHS OF CHILDREN UNDER 1 YEAR PER 1,000 LIVING BIRTHS. AVERAGE OF 5 YEAR PERIODS.

England and Wales. 1885–1904.	Large towns in Germany. (Over 15,000 pop.) 1885–1904.	Boston. 1886–1905.	New York. 1886–1905.
142	244	181	288
148	231	170	218
158	220	151	185
142	208	141	158

PUBLIC HYGIENE A SOCIAL QUESTION.

At the present time the scope of public hygiene is widening. It is becoming more plainly seen that the public health is intimately and unavoidably connected with a thousand phases of the social order. To strike at the roots of disease it is often

[3] Report of the Committee on Physical Deterioration.
[4] Rahts, med. stat. Mitt. a. d. k. Ges., 1906, x, p. 79.

necessary to get under the surface of modern life and acquaint ourselves with deep-seated human instincts. The mere formulation of the problem is, however, something, and will serve to arouse the interest of different groups of individuals whose cooperation is essential to success. That in this country we are entering on this initial phase, which must be largely educational and exploratory, is shown by the number of strong national societies that have been formed to study and advise concerning special problems, such as tuberculosis, school hygiene, the alcohol problem, the venereal diseases, and the stunting and disastrous effects of excessive child labor.

It is surely no small matter that we have come to the point where considerable groups of influential men and women are willing to undertake the task of making plain to the general public the momentous character of these questions. A concerted and persistent campaign of education backed by scientific investigation is likely to have greater weight in molding public opinion than the isolated appeals of reformers and philanthropists, however timely and well directed. The great measure of success already achieved by the crusade against tuberculosis at least serves to encourage this belief.

It is evident, I think, that with the increasing complexity of the social structure, the field of public hygiene will continue for some time to broaden. Many matters affecting the physical well-being of society which are now overlooked, ignored or regarded as a necessary part of keeping the peace, will come to be seen in their true light. I do not refer now to the improvement of the human race by selection and controlled mating, although the physical possibility of strengthening the human mechanism must be recognized and may one day be a subject for state interference, but to measures more susceptible of immediate application. We are still treating, for example, in an amateurish, desultory fashion such important questions as the influence of city dust and smoke on the respiratory tract, the effect on the nervous system of the pounding it receives from city noises and the consequences of racial mingling and amalgamation. The waste of life and the maiming of bodies

by violence, which has reached so gruesome a pass, especially in this country, is distinctly a preventable evil calling for preventive measures.

TABLE IV.

AVERAGE ANNUAL DEATH RATE FOR 100,000 POPULATION.

City.	Period.	Homicide.	Suicide.	Accident.	Total.
London	1903–4	1.1	11.2	54.2	66.5
Berlin	1900–5	0.96	29.1	59.4	89.5
New York	1900–5	4.2	22.3	108.	134.5
Chicago	1900–5	6.7	22.9	76.2	105.8
Boston	1900–4	3.5	13.7	84.9	102.1

INDUSTRIAL HYGIENE.

The time is now ripe for a fuller consideration of the interest that the whole community has in dangerous trades and hazardous occupations. The extent to which industrial injuries can be prevented by slight changes in materials and machinery is hardly realized by the general public. Strong arguments can be brought to bear in favor of industrial insurance against death and disability from accident, in favor of charging up to an industry the depreciation in men as is the custom with the depreciation in buildings and in machinery. The extra cost of a hazardous industry ought, as a business procedure, to be laid on that industry, and manufacturers will unquestionably find the public willing to assent to this view.

There are still stronger arguments, economic as well as humanitarian, for preventing or minimizing injury and disease in dangerous trades and occupations. It needs no dissertation to prove that it is less expensive as well as more humane for the community to take measures to safeguard machinery rather than to allow accidents to happen and pay the cost, whether legitimately in the form of industrial insurance or, as now, in the support of hospitals and poorhouses and in diminished industrial efficiency. The factory inspector of the State of Illinois in a plea for better protection before the State Legislature last winter brought out the facts that:

"It costs thirty-five cents to take out the raised set screw, bore a hole into the line shaft and set in the sunken set screw. And yet we had in Illinois almost 100 deaths last year in factories from the raised set screw. We know that it costs fifteen dollars to guard a woodshaper. The average life of the machine is ten years, and woodworkers will tell you their average loss is a hand for each machine every year."

In the same connection it was shown that Illinois, the third greatest industrial State in the Union, has no law protecting workers in factories, in workshops or in the building trades. At this session a bill was passed for the protection of structural iron workers on bridges and buildings,[5] but similar bills for the protection of other occupations were defeated. There is in Illinois no law providing for ventilation in shops or safeguarding machinery, hatchways, and elevator shafts. Here is a pretty definite opening for preventive and protective measures which are reasonably certain to save life, prevent disabling injuries and diseases and promote the efficiency and well-being of the body politic.

THE "POISON WORKERS."

The same thing is true of the trades and manufactures involving more or less direct contact with poisonous substances, like mercury, lead, arsenic, and phosphorus. Such dangerous industries are controlled in most European countries by elaborate regulations designed to protect the workmen against the peculiar dangers to which they are exposed. Twenty-four such industries for which special rules are in force are enumerated in England and fifteen in Germany. In the United States legal protection is almost lacking, although a great improvement in conditions has been accomplished through the voluntary action of some philanthropic and far-seeing manufacturers. In certain industries, notably those involving work with lead and phosphorus, the preventive and protective influence of simple hygienic measures is so marked that the duty of society to itself

[5] Last year in the city of Chicago, out of a total membership of 1358 in the Bridge and Structural Iron Workers' Union, 156 either lost their lives or were totally or partially disabled.

would seem to require that such measures be made obligatory. Investigation of the whole question of occupational diseases under American conditions is much needed.

EDUCATION IN PUBLIC HYGIENE.

If we grant that the collective health and physical soundness of a nation or people are at least as worthy of public concern as the conservation of other national resources, then the road is clear before us. In the present apathetic state of public opinion, as attested not only by the imperfect legal crystallization of our knowledge, but by the inadequate material and moral support given by most American communities to public health officials, one of the first steps must be educational. The clamor of modern life does not make it an easy task to shape intelligent public opinion. Many voices are crying aloud in the market place insistently and with great fervor. And yet there are indications that the preliminary work of education in public hygiene is taking effect.

The influence attained and the work already accomplished by the national societies before referred to, and especially the wide interest evoked by the Committee of One Hundred of the American Association for the Advancement of Science, to consider methods of establishing a national department or bureau of health, are signs not to be mistaken. The rapid growth of the Public Health Defense League, organized to combat all forms of quackery, charlatanism and fraud, is another instance of increasing public interest. Especially timely is the action of the American Medical Association in recommending the establishment of a Board of Public Instruction empowered to disseminate through the medium of the public press and in other channels authoritative information regarding the causes and prevention of disease. In the significant language of the report of the committee on the establishment of such a board,[6] the reading public would then come to understand "that the chief aim of the medical profession is to prevent rather than to cure

---

[6] Jour. Amer. Med. Assn., June 15, 1907, 2047.

disease." The awakening of interest must be accompanied by and is, indeed, in large part conditioned by the investigation of public health problems. As already pointed out, our knowledge of the causation and prevention of disease is in many directions far too imperfect to enable us to formulate a rational program. We cannot go to the public, except with a well-considered plan of action based on irrefragable scientific data. The outlook for advance in sanitation depends, then, on several factors: More intensive investigation of the causes of disease, especially viewing disease as a folk phenomenon, affecting large bodies of people; the effective marshalling of existing knowledge and the exposition of its bearing on the collective physical welfare; the crystallization in legal form of well-established principles and information in order to prevent as far as possible injury to some through the avarice, ignorance, or neglect of others; and, finally, the realization by the general public of the fact that the public health service is second to none in its economic value to the community. What would be thought of the individual experimenter who conducted experiments unsystematically and without reference to their significance, who employed untrained and poorly paid assistants, who neglected to keep a record of his experiments and observations, who paid little or no attention to the similar experiments of others and omitted to interpret his results? This is the sort of experimenting modern society carries on in matters of life and death.

THE PLACE OF THE MEDICAL PROFESSION.

Where is the place of the medical profession? What part ought it to take in forwarding the aims of sanitation? Selfishly, the interest of individual physicians is hardly promoted by a diminution in the amount of disease.[7] To the eternal

[7] A recent president of the British Medical Association, Dr. Henry Davy, has stated that fifty years ago his immediate predecessor in practice frequently received as much as $1500 a year for attending typhoid fever cases, but that during the past few years his own income from typhoid patients has hardly averaged $25.—Brit. Med. Jour., Aug. 3, 1907.

honor of the body of medical practitioners be it said that this view has never been entertained; that, on the contrary, physicians have been foremost in the work of preventing disease, of drying it up at the fountain head.

Some of you may remember in the antivivisection literature the grotesque libel on Pasteur, one of the gentlest and most humane men that ever lived, to the effect that he used to capture stray dogs, carry them to his laboratory, inoculate them with rabic virus and turn them loose again in the streets of Paris in order to swell his revenues by providing a supply of patients. What sound-minded, educated person does not recognize in the stupidly-minded extravagant falsity of such a statement an utter perversion of the attitude of the whole medical profession toward the causation and prevention of disease? So far from diabolically trying to increase opportunities for medical practice, the constant effort of physicians as a whole has long been directed toward detecting threatened or incipient disease and checking or cutting it off at its source, thus undermining their own livelihood.

But is this all? While the first concern of practical medicine must long continue to be for the individual, are not the conditions of modern life forcing new responsibilities on the medical profession? There are signs that the community is ready to welcome a fuller participation in the work of sanitation. I remember some years ago expressing my interest in the problems of water purification to a distinguished medical friend. I was met by the remark, "Oh, why not leave all that to the engineers?" One difficulty in the existing situation is that too much has been left to the engineers, that the working out of many problems of sanitation has fallen into the hands of men without a comprehensive understanding of the problems of disease and disease prevention. I would not be thought to underestimate in any way the splendid achievements of engineers and especially American engineers in the field of sanitation when I express my belief that the promotion of the public health is primarily a medical, not an engineering, undertaking.

TEACHING HYGIENE IN MEDICAL COLLEGES.

And this brings up the question whether a somewhat radical adjustment in the work of the medical schools will not soon be warranted, if not indeed demanded. The fact that disease may be combated not only by the cure of affected individuals, but by individual prophylaxis and by general sanitary measures, calls for a more formal and effective recognition than it has yet received. The three medical specialties of the future are curative medicine, the supervision of personal hygiene, and the direction of public hygiene; and progressive medical schools must soon begin to make provision for symmetrical development along these lines. Differentiation within the medical profession is, to be sure, already taking place, but is still in an early embryonic stage. Men trained in the methods of curative medicine drift into public health work without adequate equipment for the special tasks before them, and, while the results accomplished, thanks to the adaptability of the American character, are often surprisingly satisfactory, it can hardly be doubted that a still higher level of attainment would be reached if facilities for acquiring a suitable training were more easily come at and if more men prepared themselves with malice aforethought for the public health service.

One great obstacle to the adoption of public hygiene as a career is undoubtedly the low value heretofore set by society on proficiency and knowledge in matters pertaining to the public health. There is at present little to tempt an ambitious young man to fit himself as an expert in any phase of community medicine, since the hope of the social and financial recognition that reward the eminently successful practitioner and the assurance of a modest competence for a moderate success are alike lacking. This discouraging outlook for a livelihood and a career is the rock that has wrecked the few sporadic courses that have been launched by American universities and professional schools with the purpose of providing trained men for the public health service.

No birds were flying in the air,
There were no birds to fly.

The remedy for this unfortunate condition is plainly to make the public health service a career worthy of the best efforts and the highest aspirations. The problems of sanitation are essentially as attractive as those of curative medicine, and effective public recognition seems the one thing withheld. In the long run the standing of men that specialize in public hygiene must be determined by the community at large, but the medical profession can do much by its own position to bring about a proper evaluation of the work done in this field. As one important step better opportunities should be provided in medical schools for the training of men in public hygiene. In connection with the engineering schools of large universities or in co-operation with technical schools, courses of study leading to a special degree ought now to be planned by all progressive medical schools. Investigation of the broader aspects of disease and disease-prevention should be encouraged, not merely as affecting individuals, but as affecting the masses of mankind. Specialists in public hygiene should be supported by a united and organized medical profession and the value of such special service as they can render made unmistakably and authoritatively evident. Public opinion is now sensitive on matters affecting the public health and will lend a ready ear to professional advice. Now is the time to turn our faces to the investigation of disease on the large scale, to make clear that the prevention of disease is more worthy of consideration than the cure and, foreseeing the inevitable decline of curative medicine, to foster and develop the newer art of sanitation as an integral part of the work of the medical profession.

CANCER PROBLEMS*

JAMES EWING, M.D.,
Professor of Pathology, Cornell University, New York.

CANCER research to-day includes three separate departments:

I. THE PARASITIC THEORY.

II. THE THEORY OF CELL AUTONOMY.

III. THE MODERN BIOLOGIC AND BIOCHEMIC STUDY OF TUMORS.

I. THE PARASITIC THEORY.

Since the seventeenth century, and the time of Lusitanus, medical literature has contained numerous reports of the contagiousness of cancer. It has been claimed that the disease arises in epidemics; that it is increasing in frequency; that it exhibits, in certain localities, a significant relation to the soil and water; that it is transferred from one human being to another; that it may be inoculated into lower animals; while many have claimed to have identified the parasitic cause of its contagion.

Endemic Occurrence of Cancer.—The observations on the endemic occurrence of cancer, under current discussion, relate to the discovery of many tumor animals in the stock of one breeder, to the frequency of cancer of the eyelid in certain herds of cattle (Loeb [1]), to some peculiar cases suggesting cage infection among laboratory animals (Borrel,[2] Loeb,[1] Gaylord [3]), and, finally, to remarkable forms of epidemic cancer occurring among fish (Plehne,[4] Pick [5]). A careful examination of all these records shows that cancer may occur with remarkable frequency among aged, domesticated animals; but none of the above writers, except Plehne and Pick, have adduced any evi-

* Lecture delivered November 16, 1907.

dence which even strongly suggests an infectious origin of cancer. Similar evidence may be found to prove the infectious nature of eclampsia, diabetes, and insanity.

Cases suggesting cage infection are extremely rare. Bashford saw nothing of it in his experiments with 30,000 mice housed under conditions extremely favorable for the natural transfer of any contagion in mouse tumors. The occurrence of several tumors among the mice of one breeder is explained by the fact that the great majority of these tumors are cancers of the breast in old females long used for breeding. Other suspicious cases may safely be referred to the influence of inbreeding, old age, and uniform reaction to environment.

The cancers among fish are more significant, and their origin is not yet entirely clear. Pick has shown that thyroid cancer in artificially bred salmon trout has, in one year, carried off 7 per cent. of the fish in the Auckland Society Trout Hatchery, while Bonnett [6] reported as many as 3000 cases in one hatchery within four months. Only the older fish, two years and over, were affected, the younger ones being practically immune. In the same hatchery one variety, *Salmo fontinalis,* may be affected, while another, *S. iridescens,* may be entirely exempt. Such facts render highly improbable any parasitic factor in the origin of this disease; and Pick concludes that inbreeding and the chemical peculiarities of the water induce, first, simple goitre in large numbers of the animals, many of which later become cancerous. Likewise with "carp-pox" Plehne finds no grounds for assuming an infectious origin, but attributes the epidemics to the results of inbreeding and local factors which intensify the influence of heredity to a degree not seen in any other conditions prevailing among animals.

Cancer is said to be increasing in frequency and appearing at earlier periods of life, and some find herein evidence favoring the parasitic theory. Yet Riechelmann [7] has shown that in Berlin 20 per cent. of those dead from cancer come to autopsy without a diagnosis having been made, and a proportionate increase in the cases of cancer may still be expected from improved diagnosis. Another source of increase may probably

be found, as shown by Newsholme,[8] in the lessened mortality from infectious diseases, especially in infancy.

A relation between the incidence of cancer and the character of the soil has been discussed by many writers. In England, Haviland [9] found the disease especially frequent on the alluvial soil along the banks of rivers and rare in the older limestone regions. Behla [13] has recently brought together many interesting facts which, he believes, indicate that cancer is a water-borne disease. The occurrence of cancer-houses has been urged by Arnaudet,[11] D'Arcy Power,[12] and Behla,[10] in favor of the parasitic theory. In recent years observations, impressions, and arguments of this class have failed to maintain the interest they formerly aroused. Some of the fallacies of this line of argument have been clearly pointed out by Sticker [14] and by Prinzing.[15]

Is Cancer Inoculable?—If cancer can be transferred from one human being to another, then one of the essential characters of an infectious process will be demonstrated. No experimental evidence is needed to show that a malignant tumor may often be grafted from one part of the patient's body to another, since the several recognized modes of metastasis daily demonstrate this process. Hahn,[16] Cornil,[17] and others have needlessly performed inoculations in human beings without contributing any important scientific information, while to-day such experiments are being successfully performed on animals for legitimate objects in many laboratories.

That cancer may be transferred spontaneously by contact from a cancerous surface to an apposed abraded or inflamed surface in the same subject also appears to be a fact, but the cases demonstrating such an event in man are extremely rare. In order to demonstrate such a transfer, it must be demanded that the transferred tumor shall exhibit a structure similar to that of the original, but different from that spontaneously arising in the infected tissue. Epithelioma arising at the same point on the upper and lower lips always offers the possibility of the spontaneous origin of both tumors. It is extremely difficult to find a reported case, free from reasonable objections,

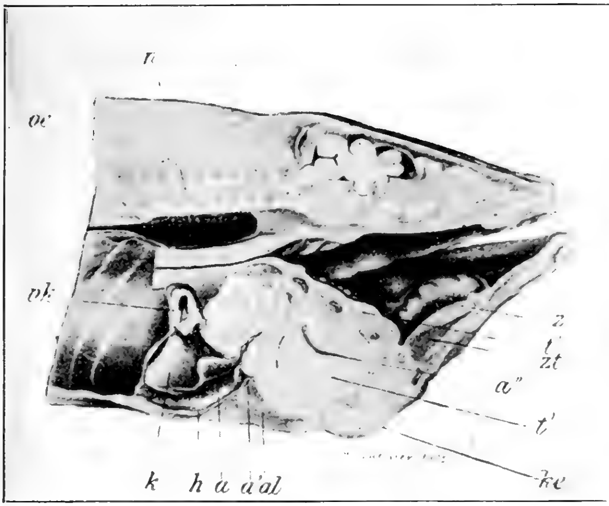


Fig. 1.—Thyroid carcinoma of trout (after Pick). *a a′ a″*, aorta; *t′* tumor mass; *t″*, tumor invading pharynx; *z*, tongue; *k*, cardiac chamber; *œ*, œsophagus; *n*, kidney; *al*, compresser ventral muscle.

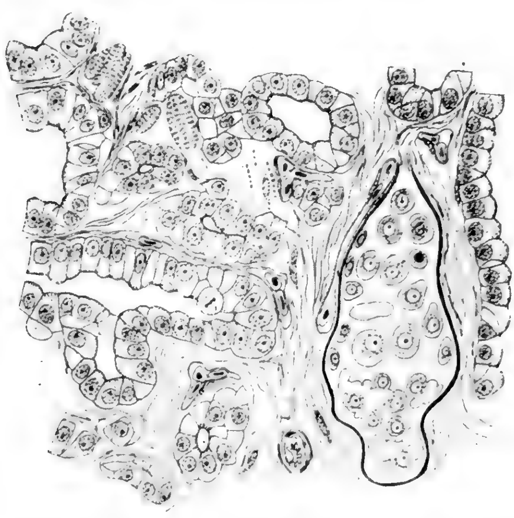


Fig. 2.—Adenocarcinoma of trout invading branchial arch (after Bashford).

demonstrating the transfer of cancer by contact of external surfaces. A typical but still uncertain instance is the case of Hartmann and Lecene [18]—that of a cylindrical-cell cancer of the uterine cervix with cylindrical-cell cancerous ulcer of the adjacent vaginal mucosa. As the vaginal ulcer did not show the usual type of squamous-cell epithelioma, the authors concluded that the growth must have been inoculated from the cervix. Yet there are several types of cancer of the vagina, and some, especially those of plexiform arrangement, closely resemble cylindrical-cell cancer. Moreover, the long duration of this case, four years, offers opportunity for metastases, for which the vaginal mucosa is a common seat. Yet the recent results of inoculation of tumors in lower animals render it highly probable that autoinoculation by contact of mucous surfaces may occur in man. One of the recognized modes of metastasis is through the passage of fragments of tumor along the œsophagus or ureter (Butlin [19]) with implantation lower down in stomach or bladder.

Of much greater significance is the question of the inoculability of cancer from one human being to another healthy subject. Here the element of a comparatively refractory soil is introduced. The studies on tumors of lower animals show that this factor is of extreme importance, and they also show that the rules observed with one tumor and one animal cannot be applied safely to other tumors and other animals. Hence the inoculability of cancer among human beings must be considered entirely from the observations on the human subject. The invariable immunity of surgeons to inoculation by the tumors on which they are operating has always justly stood as strong evidence that cancer is never spontaneously transferred from one human being to another. Alibert [20] inoculated five human cancers on himself and his assistants with negative results. I am unable to find any satisfactory report of the transfer of a malignant tumor from one human being to another. The alleged cases of infection collected by Smith and Washbourn,[21] Park,[22] and Behla [13] demonstrate only the dominating influence of the preconceived notions of the observers, since many essayed

to prove not only the communicability of cancer among human beings, but the frequent transfer of the disease from man to lower animal and from the lower animal to man. It is noteworthy that observations of this class have largely disappeared from recent literature. The inoculability of warts appears to have been demonstrated by Lanz,[23] who produced a series of warts in the skin of his gardener's hand by implanting pieces of such growth taken from a human subject. Their genuine neoplastic nature may be doubted.

The cases of so-called "*cancer à deux*" have figured prominently, from time to time, but in none has the contagion been conclusively shown. Demarquay [24] collected 134 cases of cancer of the penis, in only one of which infection by coitus appeared possible. Of the twenty-seven cases of such infection collected by Guelliot [25] none are beyond question.

Is Human Cancer Inoculable in Lower Animals?—Among the very numerous attempts to inoculate lower animals with malignant tumors from human subjects, there has been for many years a small proportion of instances where the experimenter claimed success. The vast majority of such experiments have undoubtedly failed. Pianese [26] mentions twenty reports of failure by as many observers in a large total of experiments. Many others exist in the literature, and probably still other negative results have never been published. The alleged successful results have, with a few possible exceptions, not been able to meet the conditions required for a successful demonstration. Some of the exceptions appear to deserve mention.

In 1894 Boinet [27] inoculated sixty animals with fragments of human cancer, and in one case from a cancer of the penis produced multiple nodules of the same histologic character in the peritoneum and along the spinal column. One may refuse to believe, but one cannot successfully refute the genuineness of Dagonet's case,[28] 1904, in which the intraperitoneal inoculation in a white rat of a comminuted epithelioma of the penis was followed in fifteen months by voluminous tumors of the same histologic type in the peritoneum, spleen, and liver. Dagonet's later cases (p. 552) were less satisfactory, as the alleged tumors

FIG. 3.—Liver, spleen, omentum, and microscopic section of Dagonet's transplanted human epithelioma in a rat.

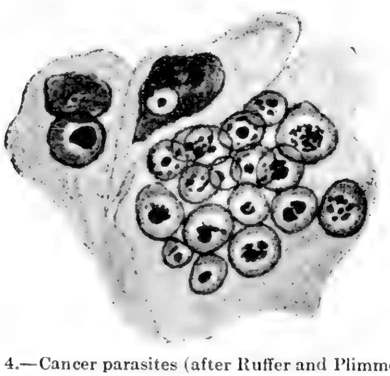


FIG. 4.—Cancer parasites (after Ruffer and Plimmer).

produced were atypical and of different type from that injected. Leopold[29] also claims to have transferred a malignant tumor of the human ovary by intraperitoneal inoculation in a rabbit.

Jürgens,[30] in 1896–97, was quite sure that he had succeeded in transplanting human melanomata into rabbits. Werner[31] transplanted a human carcinoma of the jaw into an old dog, and claims to have seen the development of a genuine malignant epithelioma at the site of inoculation, with extensive metastases in the peritoneum.

While these isolated reports are inadequate to prove the occasional inoculability of human cancer in lower animals, they cannot safely be discarded as mistaken observations. Orthodox opinion was once firmly set against the possibility of transferring cancer among lower animals of the same species. It would seem necessary, therefore, to regard the question of transference of human cancer to lower animals as undetermined, while urging that the weight of evidence is strongly against such a possibility. Metchnikoff and Grünbaum[32] failed in several attempts to transfer human cancer to higher monkeys.

That some cancers of lower animals may be distributed readily among members of the same species is one of the chief results of the recent experimental study of tumors, and the subject will be reserved for consideration later.

Certain malignant tumors having been shown to be inoculable, the question remains, what does this fact prove regarding the etiology of such tumors? The unreserved answer to this question must be that it proves nothing. Leyden[33] has ventured to claim that there is no distinction between inoculation and infection, and that the inoculability of certain cancers demonstrates their infectious nature and an extrinsic parasitic cause. It is, however, the most patent distinction between tumor metastases or inoculation and known infectious diseases that the new growth develops from the transplanted cells, from factors inherent in those cells, whereas all known parasitic micro-organisms produce lesions in which the cells are derivatives of the host's tissue. In tuberculosis the infecting agent is the tubercle bacillus, while in cancer all available evidence

points distinctly to the cancer cell as the infecting agent and the homologue of the tubercle bacillus. Borrel,[34] a consistent advocate of the parasitic theory, clearly accepts this distinction, and admits that inoculability of cancer proves nothing for the parasitic theory; but he claims that the continued growth of tumor cells does not disprove the existence of a parasite apart from the cells, a contention which need not here be disputed.

However important may be the studies so far reviewed for the general problem of the biology of tumors, it has long been evident that they have only a secondary and often a rather distant bearing on questions of etiology.

Recognition of the inadequacy of such evidence to solve the problem has always led the advocates of the parasitic theory to attempt the direct demonstration of the parasite of cancer.

History of the Cancer Parasite.—The search for the cancer parasite has been a chaotic chapter in medical research. The investigators who have undertaken these studies have been of every degree of competence; and, inspired by the lively hope of results of sensational value, and guided by an imperfectly grounded theory, the majority seem to have substituted easy credulity for critical common sense and to have accepted vague suggestion as demonstrative proof. Hence it is little wonder that micro-organisms of every variety, according to contemporaneous interests, have at one time or another been widely accepted as the cause of cancer, even by experienced authorities of the highest standing. In the early nineties it appears to have been a question, not so much as to the infectious origin of cancer, but rather as to which of the many parasites was the real causative agent.

After the discovery of the specific agents in many infectious diseases, especially in the infectious granulomata, several observers claimed to have discovered specific bacteria in malignant tumors. These claims were with difficulty set aside, to be succeeded by an era, still continuing, of search for a protozoon cause of cancer. Later arose a tendency to attribute to blastomycetes an etiologic relation to malignant tumors; and,

lastly, some have urged the claims of mycetozoa. A partial list of the various structures or micro-organisms at one time heralded as the cancer parasite, with name of author and date of publication, follows:

CANCER PARASITES.

BACTERIA: Bacillus of Rappin,[35] 1886; Scheurlen,[36] 1887; Francke,[37] 1888; Lampiasi,[38] 1888; Koubassof,[39] 1889.
Micrococcus neoformans, Doyen,[40] 1902.
COCCIDIA: Coccidium of Darier,[41] 1889; Albarran,[42] 1889; Thoma,[43] 1888; Sjobring,[44] 1890.
Coccidium sarcolytum, Adamkiewicz,[45] 1892; Soudakiewitsch-Metchnikoff,[46] 1892; Monsarrat,[47] 1905.
SPOROZOA (unclassified): Bird's-eye inclusion, Foa,[48] 1891; Plimmer's bodies, 1892.
Sporozoon, Ruffer,[49] 1892; Sawtschenko,[50] 1893.
Amœbasporidium, L. Pfeiffer,[51] 1893.
Rhopalocephalus carcinomatosus, Korotneff,[52] 1893.
Sporozoon, Kourloff,[53] 1894; Bosc,[54] 1897.
Hæmatozoon, Kahane,[55] 1894.
Cancriamœba macroglossia, Eisen,[56] 1900.
Leydenia gemmipara, Schaudinn,[57] 1896.
Intranuclear parasite, Schuller,[58] 1901–4.
BLASTOMYCETES: *Saccharomyces neoformans,* Sanfelice,[59] 1896; Plimmer,[60] Leopold,[61] Roncali,[62] Bra.[63]
Russell's fuchsin bodies.[64]
Mucor racemosus, Schmidt,[65] 1906.
MYCETOZOA: *Plasmodiophora brassicæ,* Behla,[66] Podwyssoski,[67] Feinberg,[68] Gaylord,[69] Robertson and Wade,[70]
SPIROCHÆTÆ: Gaylord,[71] Calkins,[72] 1907.
Cyanide-fast bodies, Robertson,[73] 1907.

In reviewing this list it must not be supposed that the claims of these various pseudoparasites were urged without abundant evidence of a certain type. Many of the observers believed they had isolated their micro-organisms in pure culture and had produced tumors with the cultures. The entire realm of zoology and botany was laboriously searched for parallel protozoon or vegetable forms, and few of the investigators ventured to announce their discoveries without the endorsement of some distinguished biologist. Many years of systematic and toilsome study were devoted by some observers, notably Sanfelice, to the support of their beliefs. One may well pause, while viewing this battleground, to acknowledge that no other problem of

medical science has resisted such strenuous efforts directed toward its solution.

At the present day it cannot be said that much of positive value remains from the search for the cancer parasite. Pathologic anatomists, who are most occupied with the nature of the tumor process, have seldom actively engaged in this search on account of objections to the parasitic theory, and in their opinion its results have been wholly negative. No parasite has yet been discovered in cancer.

The occurrence of peculiar cell inclusions in malignant tumors had long been known and interpreted as a feature of cell degeneration before the parasitic theory came into prominence. Virchow,[74] among others, so interpreted many of these bodies and warned against the hasty conclusions regarding them by adherents of the parasitic theory. Russell's fuchsin bodies were early described by Fox[75] and later by Klein,[76] and Lubarsch[77] in 1892 showed that they are present in many normal tissues. Darier's psorosperm of Paget's disease was openly repudiated by its discoverer in 1904.[78]

Among enthusiastic exponents there has never been the slightest approach to unanimity of opinion regarding the identity of the true parasite, its unity or multiplicity, its position in the cytoplasm, nucleus, or intercellular spaces, nor as to its biologic position.

Stroebe,[79] reviewing the basis of the parasitic theory at the height of its popularity, 1894, found almost as many different parasites and theories as adherents of the theory; presented the views of seventeen open sympathizers with the theory who could not find sufficient evidence in its favor; abstracted the reports of many competent and some very experienced observers who pronounced against the parasitic nature of all cancer bodies; and with Lubarsch pointed out a score of degenerative processes in tumor cells which certainly contributed to the numerous class of cell inclusions, and, in all probability, fully accounted for their occurrence.

By a process of attrition in the hands of friends the possible parasitic forms were reduced to a single body—the "bird's-eye

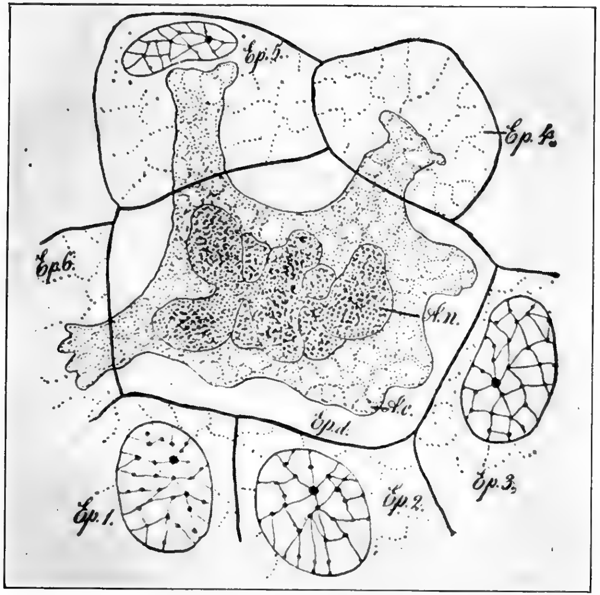


FIG. 5.—Cancriamœba macroglossia (after Eisen). *A.c.*, amœba; *A.n.*, nucleus of amœba; *Ep.*1–6 epithelial cells; *Ep.d.*, destroyed epithelium.

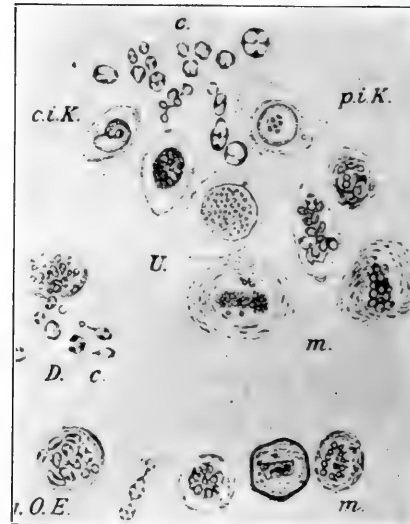


FIG. 6.—Schuller's intranuclear parasite of carcinoma and sarcoma. *U*, uterine cancer; *D*, intestinal cancer; *p.i.K.*, intranuclear parasite; *c.i.K.* chromatin bodies in nucleus; *c*, chromatin bodies free; *m*, mitosis-like grouping of chromatin bodies; *j.O.E.*, young organisms.

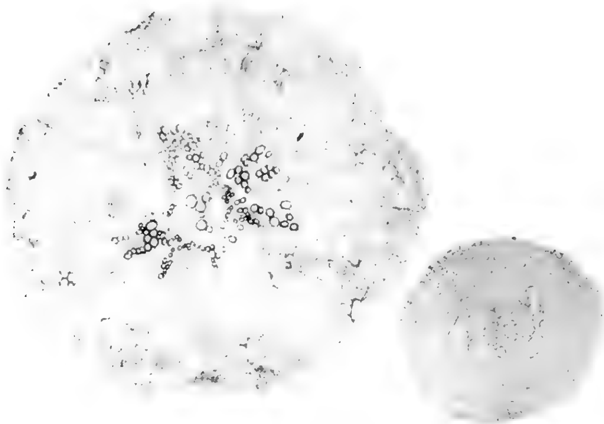


Fig. 7.—Normal and hypertrophic plant root infected with Plasmodiophora (after Woronin).

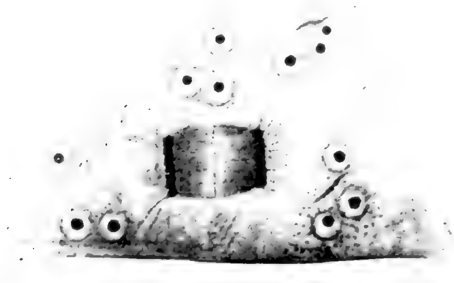


Fig. 8.—Dividing vegetable cell infected with Plasmodiophora.

inclusion"—first described by Langhans and correctly interpreted in 1886. Feinberg,[68] urged by Leyden, made a final effort to detect in this body and its supposed derivative, the Russell fuchsin body, morphologic characters demonstrating its parasitic nature; but Feinberg's criteria, double contour, nucleus surrounded by a clear zone, and metachromatism, were promptly and authoritatively discarded by O. Hertwig,[80] and Lubarsch [81] pronounced these characters to be positive evidence of a degenerative product. Foa, who first cautiously emphasized the importance of the bird's-eye inclusion of cancer cells, abandoned his belief in its parasitic nature at the Fourth International Medical Congress in Rome.

In this condition the question of intracellular parasites in cancer remains to-day, and one must subscribe to the conclusion of Lubarsch,[81] 1902, that no specific micro-organism has been demonstrated in cancer or in any other autonomous new growth.

In regard to the relation of mycetozoa to cancer, it must be urged that according to von Tubeuf,[82] the histology of club-root, the disease of plants produced by *Plasmodiophora brassicæ,* is not that of a true neoplasm, the tumor resulting principally from distention and degeneration of infected cells surrounded by an area of inflammatory overgrowth; that the behavior of *Plasmodiophora* in plants is widely different from that of any suspicious structure in malignant tumors; and that the resemblance between the spores of *Plasmodiophora* and the bird's-eye inclusion is both affirmed and denied, while a resemblance does not assure identity.

With regard to blastomycetes, the researches of Busse,[83] Rabinowitsch,[84] Sternberg,[85] Richardson,[86] Nichols,[87] and many others have established the following conclusions:

1. Blastomycetes are rarely cultivable from protected tumors; but when present and living there is no ground for supposing, as does Sanfelice, that they cannot readily be demonstrated by culture.

2. In sections of tumors, blastomycetes, or structures resembling them, are not always present; and the identity of Plimmer's bodies or Russell's fuchsin bodies with blastomycetes liv-

ing (Plimmer) or dead (Sanfelice) has not been established, but has been rendered improbable.

3. When present in tumors the number and distribution of yeasts do not favor the belief that they have any essential relation to the tumor, but rather that they represent a secondary infection only (Mafucci and Sirleo,[88] Meser[89]).

4. Elaborate studies of yeasts from many sources have failed to show any that are capable of producing tumors, and few that are pathogenic for animals; and have fully determined that the pathogenic action strictly attributable to them falls within the limits of an inflammatory process. A possible exception to this statement may be found in the results of Schmidt,[65] who is said to have produced a genuine malignant tumor by injections of a yeast, *Mucor racemosus*. His results have not been verified.

Spirochætæ in Tumors.—Some interest has been excited by the discovery by Gaylord[71] and Calkins[72] of a single type of spirochæta, in ten consecutive cancers of the breast, in mice obtained from three different localities, and in all of sixteen transplanted tumors from these strains. Gaylord found these organisms in the connective tissue and between the tumor cells of the growing edge, and he reports that the more virulent tumors contained the greater number of organisms. Borrel[90] had previously reported the discovery of many spirochætæ in two mouse tumors, without attributing to them etiologic significance, and Wenyon[91] has shown that mice are susceptible to blood infection by spirochætæ. Tyzzer[92] has given the clue to the interpretation of these results by finding several tumors in mice free from spirochætæ, and by discovering large numbers of spirochætæ resembling the spirochæta of Gaylord in the organs and mediastinum of two mice dying several weeks after unsuccessful inoculations with tumors containing spirochætæ.

In human cancers Mulzer[93] and Lowenthal[94] found spirochætæ on ulcerating surfaces. In a series of thirty-five human tumors and twenty-five in the dog, I have found spirochætæ only on ulcerated surfaces or in necrotic areas. By treating their tumor growths with KCN Gaylord and Clowes have suc-

FIG. 9.—Intracellular bodies in the "contagious epithelioses." (Photo. by Dr. Leopold Jaches). (1) cancer bodies (after Sawtschenko). (2) *Molluscum contagiosum.* (3) Vaccine body in Klaatsch preparation of rat's cornea (photograph of drawing). (4)Measles; intracellular bodies of cutaneous epithelium. (5) Clavelée (after Bosc). (6) Trachoma (after Halberstädter and Prowazek). (7) Negri bodies of rabies (after Williams and Lowden). (8) Contagious epithelioma of birds (after Michaelis).

ceeded in passing their infected mouse cancers through several generations entirely free from spirochætæ. It appears, therefore, that spiral organisms must be added to the list of occasional saprophytes occurring in tumors.

Acknowledging complete failure to discover a specific parasite in cancer, some exponents of the parasitic theory are endeavoring to support the theory by collateral evidence, which is largely histologic. This interesting line of inquiry is, in the minds of many, a promising field, and it must be admitted that its evidence is far more direct than that derived from observations on the general occurrence of cancer. The results of this work are effectively presented by Borrel.[34]

It has been shown that the cell inclusions of cancer have homologues in many other diseases which are highly infectious. According to Borrel, the psorosperm of Darier,[41] the cancer inclusions of the common types, the vaccine bodies of Guarnieri,[95] the intracellular bodies of *Molluscum contagiosum,* and those described in *clavelée* by Bosc,[96] in the contagious epithelioma of birds by Michaelis,[97] in carp-pox by Lowenthal,[98] and in trachoma by Halberstädter and Prowazek,[99] are all cellular degenerative products which, however, are specific for these diseases and indicate a common type of etiologic agent. The real infecting agent Borrel[100] believes he may have discovered in the contagious epithelioma of birds in the form of a *congeries* of minute cocci staining by Loeffler's flagellar method and forming a mass lying beside the specific cell inclusion. Lipshütz[101] has described the same minute bodies in the filterable virus of *Molluscum contagiosum,* and Burnett[102] in a human case, while Borrel[103] identifies them in vaccinia.

It is too early to draw conclusions regarding the significance for the contagious epithelioses of these interesting observations, but there need be no hesitation in pointing out the fundamental differences between the contagious epithelioses and true cancers. Besides the patent differences in gross and microscopic appearance of the lesions, in the clinical courses which vary from malignant variola to a chronic cancer lasting for many years, in the immunity promptly established in the epithelioses, and in

the filterability of their viruses, all the infectious epithelial processes lack that capacity for limitless infiltrative growth which is just the essential and mysterious feature of malignant tumors. To assume a relation between cancer and any of these contagious epithelioses is to introduce an ill-founded hypothesis, which renders extremely uncertain the value of results obtained in this field.

It is not necessary, however, to deny all relation between parasites and malignant tumors. In one sense certain well-known micro-organisms seem to act as indirect exciting agents of tumors. One of the most important facts in the etiology of tumors is that many malignant neoplasms develop after long-continued inflammation which is caused by external irritants or parasitic micro-organisms. Inflammatory hyperplasia passes by insensible gradations into a neoplastic growth. Epithelioma of mucocutaneous junctions is usually the sequel of chronic irritation; cancer of the breast is generally preceded by chronic mastitis; hypernephroma often by renal calculus; cancer of the stomach by simple ulcer. Considering the frequent development of epithelioma after lupus or tuberculosis of the skin, and of sarcomatoid hyperplasia of lymph-nodes in tuberculosis, it might be said that the tubercle bacillus is in one sense a cancer parasite, since in some cases it has a special tendency to induce neoplastic hyperplasia. But at some point in the course of the cellular hyperplasia the tubercle bacillus gradually or suddenly disappears from the field and the tumor process continues from its own intrinsic forces. In the same way *Spirochæta pallida* seems to have a peculiar tendency to favor the development of epithelioma of the tongue after syphilitic psoriasis, but the spirochæta does not follow the invading epithelial cells.

In the lower animals there are examples of neoplasms in which the continued presence of a parasite is more essential to the progress of the tumor, as in the coccidiosis of the rabbit's liver, in the vesical cancer following Bilharzia disease, and in the tumor-like processes produced experimentally by certain yeasts (Schmidt).

In none of these conditions does the parasite seem to act

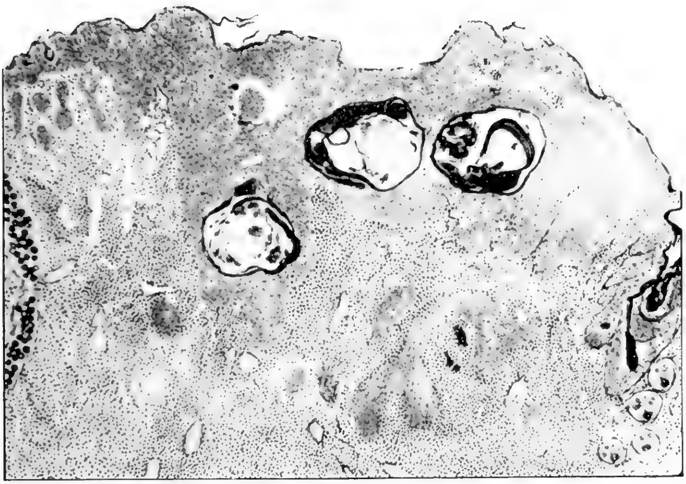


Fig. 10.—Epithelial tumor in ear of rat. Acari in Malpighian tissue (after Borrel).

directly in producing the tumor, as it does in causing its specific inflammatory reaction; but the tumor develops as a late sequela, from secondary factors set up by the long-continued growth of the parasite. Adenoma of the liver follows coccidiosis only after protracted distention of the bile-ducts.

Now it is fully recognized that the initiation of a tumor process is an entirely separate problem from its perpetuation when once established. We already know of many external irritants and micro-organisms which are concerned with the inception of tumors, but human ingenuity has so far failed to find any trace of an external irritant or parasite continuing throughout the course of a malignant neoplasm.

These considerations would lead one to conclude that external irritants and parasites are concerned only with the inception of tumors, and then indirectly; they suggest that certain irritants and parasites may be peculiarly effective in producing tumors; they suggest that in some tumors, especially in lower animals, neoplastic hyperplasia may depend in varying degrees on cellular irritants; they leave the way open for the discovery of new irritants and parasites concerned with the beginnings of tumors; but they shut the door against the theory of a special cancer parasite and of the necessity of a continuous irritant propagated by a micro-organism throughout the course of a malignant tumor.

II. THE THEORY OF CELL AUTONOMY.

The theory of cell autonomy is the product of the best thought on the nature of tumors, and in the minds of many offers a virtual solution of the problem. It is a growth from many sources and is greater than the mind of any one contributor to it, being firmly founded on the sum total of clinical observations and supported by assured principles drawn from many collateral sciences. It is not a finished theory, but has an ever-broadening scope determined by the progress of the sciences on which it is founded.

It is not a popular theory, being difficult of comprehension in many of its phases, requiring concentrated study for its full

understanding, and long familiarity for the proper appreciation of its force. The longer one studies it the more satisfactory it becomes, and this conviction lies at the bottom of the antagonism which pathologic anatomists feel for any theory or research which ignores its significance.

The germ of the theory of cell autonomy appeared in the studies of Remak [1] and Thiersch,[2] who traced the antagonistic relation of epithelium and connective tissue throughout embryonal development and detected its significance for the problem of cancer. Epithelium seemed to be everywhere the dominating embryonal tissue, and in the formation of organs seemed to cease growing when it met sufficient resistance from the connective tissues. Thiersch found in the weakening of membrana propria and stroma in the atrophying breast a relief of tension capable of reawakening the formative tendencies of gland cells, with their longer span of vital activity; and thus cancer developed. The decay of the connective tissues he regarded as senile involution and the growth of cells as degenerative proliferation.

The idea of cell autonomy appears more clearly in Cohnheim's theory. The groundwork of this theory had been laid many years before in the observations of Lobstein,[3] Remak, Thiersch, and Waldeyer [4]; and the theory was first definitely stated by Durante,[5] who in 1871 demonstrated that the cells of pigmented moles giving rise to malignant sarcomata are of embryonal type, whence he concluded that all tumors arose from embryonal cells. Cohnheim [6] in 1874 collected many facts regarding the large class of mixed and heterologous tumors, contending that they arise from masses of complex or simple tissue misplaced during embryonal development. Cohnheim believed that tumors also develop from small groups of cells which have retained their embryonal characters, but need not necessarily be misplaced. The idea of the embryonal character of the cells appeared to him essential. He believed that most of the embryonal cells result from over-production, chiefly at the period when the definite rudiments of the viscera are being formed from the germ layers; and he suggested that the superfluous cells were either distributed throughout the tissues or were

gathered in groups at certain points, such as the mucocutaneous junctions. The sudden development of the cells into tumors he referred chiefly to changes in the blood supply.

The entire group of mixed tumors and the simple heterologous growths illustrate the basis of Cohnheim's theory. When one explores the group of teratomata there seem to be all transition stages from the complex sacral teratoma containing parts of the gastro-intestinal tract and the respiratory and nervous systems, up to abortive parasitic implantations containing parts of organs or limbs, and even up to such phenomena as the Siamese twins. Likewise, when one passes downward through the complex heterologous tumors of the parotid to the simple heterologous growths which arise from small groups of cells misplaced in later embryonal life, such as adenoma of a supernumerary breast, it seems but a step to regard carcinoma of the breast as arising from embryonal cells, misplaced or not, and the conception arises that the whole question of tumor growth is one of the mechanics of development. According to both Critzmann [7] and Beard,[8] the entire history of oncology from cancer to twins is explained by the inclusion at various times and to various degrees of one egg cell or primary germ cell in another.

Cohnheim's theory had two principal deficiencies. It assumed the existence of embryonal cells where they cannot be demonstrated, and it failed to explain satisfactorily why the embryonal cells suddenly start on their neoplastic course. Later discussion has abandoned the hypothesis of embryonal cells as a necessary basis of tumors, and has endeavored to explain on other grounds why certain cells begin to multiply. Yet oncology still bears, and always must carry, the stamp impressed by the discovery of the fact that embryonal cells possess in unusual degree the essential factors in tumor development.

The majority of tumors, however—in fact, the most malignant—do not, so far as is known, grow from embryonal cells. On the contrary, there is good reason to believe that many tumors develop from adult cells. Yet, while the English Commission has elaborately shown that cancer throughout the ani-

mal kingdom is pre-eminently a disease of old age, many embryonal tumors develop late in life. To account for the limitless growth of adult cells the theory of cell autonomy introduces the conception of tissue tension, which has been most fully stated by Ribbert.[10]

Ribbert endeavors to explain the development of tumors solely by the removal of certain cells from the influence of tissue tension by which their growth is normally restrained. He abandons Cohnheim's theory that the disturbed cells must be embryonal, claiming that the regenerative capacities of adult cells are quite sufficient to account for all the characters of malignant neoplasms. He has laboriously endeavored to produce tumors experimentally by separating adult cells from their connections, but without definite success; and he brings evidence to show that the inflammatory growth of connective tissue separating epithelial cells is the usual method of freeing from tissue tension the cells which go on to develop tumors. In psoriasis of the tongue and early adenocarcinoma of the stomach he finds fibroblasts growing between the epithelial cells and snaring them off from their normal connections. In this form Ribbert's theory is supported by a host of observations. Indeed, as the misplacement of adult cells must be very frequent, Ribbert fails to explain why tumors are not more numerous; and in the minds of many he inadequately provides for the particular forces precipitating the misplaced cells into the malignant process. He also failed to explain the frequent development of malignant tumors where no such displacement can be supposed to exist; and he ignored the fact, pointed out by Hansemann, that cells which seem to remain in their proper relations may still show the morphology of tumor cells.

Recently Ribbert has modified and expanded his views in important directions. He abandons the idea that the cells must necessarily be misplaced, holding that cellular changes in the supporting connective tissue are sufficient to disturb the physiology of epithelium and incite a tumor process. Studying early carcinomata, he emphasizes the importance of the precancerous stage. Here the initial change is a proliferation of subepithe-

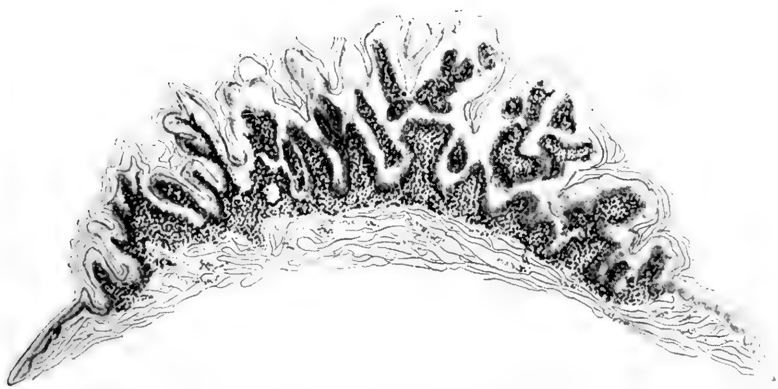


Fig. 11.—Beginning epithelioma of lip. Thickened epithelial papillæ over a layer of dense cellular infiltration (after Ribbert).

lial fibroblasts, with the production of new tissue which disturbs the tension between epithelium and connective tissue. This proliferation is of inflammatory origin and may be referable to irritation by metabolic products or secretions of the epithelium. The epithelium then reacts, also by proliferation, but the growth follows the analogy of normal gland formation; while, owing to a process of adaptation to the abnormal environment and loss of function, the atypical structure of cancer results.

According to Ribbert, tumors grow out of their own cells exclusively, never from the cells in contact with them; and since at all recognizable stages the tumor cell series is isolated, it follows that the cells of origin are isolated. To account for the primary segregation of the originating cells, he accepts all the known forms of separation of cell groups during embryonal life. The observations of Borrmann,[11] Meyer,[12] Lubarsch,[13] and others have shown that foci of isolated superfluous cells are vastly more frequent than was ever imagined in Cohnheim's day. He also appropriates a large number of structural anomalies without displacement of cells, which may be explained by reference to the history of phylogenetic and ontogenetic development. The peculiar locations and structure of a large number of tumors suggest spasmodic reversions to the anatomic conditions of prehistoric man or of other, once more closely related animal species.

Thus, the fusion of multiple reniculi, in phylogenetic development; the coalescence of multiple uteri and breasts; the reduction in length of stomach, intestine, appendix, and colon; the loss of lymphoid tissue in the relatively narrow human cæcum; and the elimination of hair and sebaceous follicles in the face, etc., all lay a significant foundation for the atavistic growth of tumors in many organs. It would be a pity if the comprehensive view of the etiology of tumors which is revealed in the phylogeny and ontogeny of the human body were destined to be replaced by the crude conception of an invading parasite.

On this broad basis of embryonal misplacements, developmental history, and suppressed potencies, the theory of cell

autonomy proceeds to consider the neoplastic growth of predisposed cells. In order to appreciate how far the theory can explain malignant tumors, one must examine more closely the factors entering into the conception of tissue tension.

Conception of Tissue Tension.—All the forces which control the multiplication of tissue cells and maintain the tissue in a physiologic condition are included in the idea of tissue tension. At least four such factors are known, three of which are recognizable as physical forces, while the fourth, more complex, cannot be wholly identified as purely physical. These factors are:

1. Mechanical pressure of cells on each other.
2. The influence of specialized functions.
3. The distribution of nutriment.
4. Organization.

Under each of these heads belong important contributions to the theory of cell autonomy.

Mechanical Pressure of Cells on Each Other.—The theory of Thiersch emphasized the importance of the mechanical restraint of epithelium by the supporting connective tissue. This theory deals with one of the factors which may often favor the growth of tumors, but it is obviously incapable of being extended to all tumors or of adequately accounting for any. Mechanical pressure is a powerful factor in the spontaneous regression of tumors. Regressing tumors are usually surrounded by a connective tissue capsule, and Loeb[14] found that when he excised a portion of such a regressing tumor in a rat and replanted it in the same animal it immediately began to grow rapidly.

Influence of Specialized Functions.—The energies of cells are normally divided between proliferation and specialized function, between work and growth, both being limited by blood supply. In most organs certain groups of cells are set apart for growth, and from these are derived the more specialized functionating cells. Examples are the germ-centre cells of lymph-nodes, the cells at the bases of intestinal villi, and

the basal cells of the epidermis; and it is just from these cells, subject to marked variations of the demands for growth, that tumors arise. It is clear that deficient demands for function on the part of derived cells would leave their energies unconsumed and further available for growth. These conditions surround the inception of cancer in the atrophying breast. Adami [15] has ably presented the general importance of this point of view, designating the tumor process as the cumulative "habit of growth replacing the habit of work."

It may be objected that there is no warrant for the assumption that actively functionating cells can suddenly turn their energies into growth. Yet the fact that they do so is prominent in the history of tumors, as in the carcinomatous changes in the actively functionating goitre and in many instances of inflammatory hyperplasia becoming neoplastic.

Oertel [16] has pointed out that excessive activity of one function is observed in degenerating cells, as in the paralytic hypersecretion of glands and in the excessive secretion of bile in degenerating liver cells. He claims to have traced the development of cancer of the liver from degenerating liver cells, and justly supposes that if the specialized functions of degenerating cells may be performed in excess, then an excessive capacity for growth may be expected in such cells. His theory that tumor growth is a form of cellular degeneration has been held by Thiersch and Benecke,[17] is supported by many peculiarities in the history of tumors, and is a valuable working hypothesis.

Distribution of Nutriment.—A vast number of clinical and experimental studies has established the importance of blood supply both for the inception and progress of tumor growth and for the physiologic proliferation of cells. It is true that hyperæmia alone does not explain tumors; but nutrition is one of the important elements in tissue tension, and when its distribution is disturbed one of the essential factors of tumor growth is provided. An explanation of the excessive capacity of tumor cells to absorb nutriment would unravel a great mystery in the physiology of neoplasms. An extremely important bearing of this factor has been found by L. Pick [18] in the rela-

tion of corpus luteum secretion to chorio-epithelioma. In 1895 Marchand [19] found that in a large proportion of cases of this very malignant tumor both ovaries show hyperplasia and cystic distention of the corpora lutea. It has been shown experimentally by Fraenkel [20] that the persistence of corpus luteum cells is essential to the development of the placenta, and the conclusion at once arises that excessive activity of these cells is responsible for the destructive proliferation of the chorionic epithelium. Here we have an instance of a specific internal secretion presiding over the growth of an organ and its excessive production associated with a malignant tumor of that organ. It has been objected that cystic ovaries are not always found with chorio-epithelioma, but the theory need not fall on that account; while Patellani [21] finds that, up to 1905, 91 per cent. of the fully reported cases of chorioma were associated with bilateral cystic ovaries.

The theory of specific internal secretions presiding over the nutrition of specific tissues has, possibly, a wide application in physiology; and this theory, combined with that of Cohnheim, with which it ranks in importance, may be found to cover a large group of malignant tumors. Ehrlich has applied the theory of a specific nutritive substance, not itself the nutritive molecule, but presiding over nutrition, to explain the interesting results of his zigzag transplantation of mouse tumors from mouse to rat and back.

Organization.—The most important element in tissue tension is that designated as organization. This is itself a complex conception; but in it we approach most closely to the true meaning of normal and of tumor growth, and here is found the most hope that a final explanation of the tumor process may be attained.

If the head and several segments of an earthworm are cut off, the body regenerates a head. If the leg of a crustacean breaks off, a new leg is regenerated at or near the breaking joint. If the head of a flat-worm is cut off and the stump split for a short distance down the middle, two heads develop if the split ends are held apart, but only one if the split ends

Fig. 12.—Choriocarcinoma with bilateral cystic ovaries.

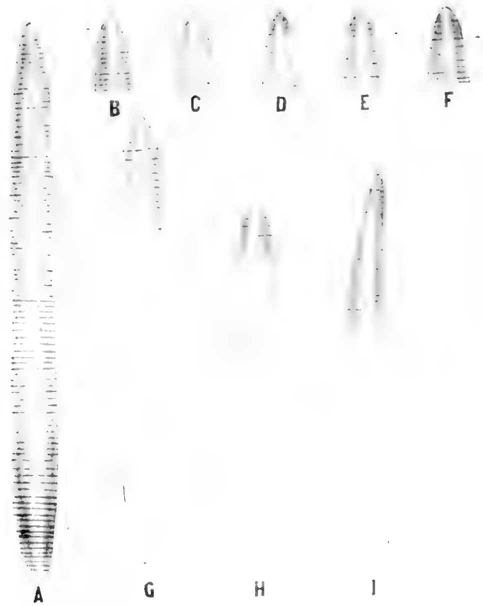


FIG. 13.—Regeneration in earthworm. *A*, normal worm. Remaining figures indicate levels of section with resulting regeneration (after Morgan).

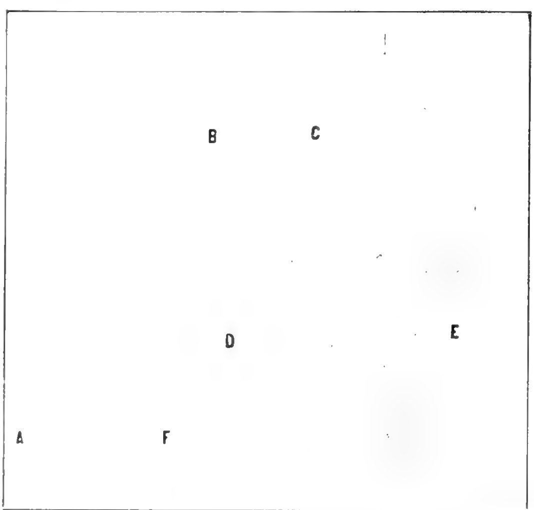


FIG. 14.—Regeneration in Antennularia (after Morgan). *A*, normal growth; *B*, growth of transplanted stem in upright position; *C*, in inverted position; *D*, *E*, in oblique positions; *F*, in horizontal position

coalesce. If the head of an earthworm is cut off, a new head develops; but if the severed head is immediately replaced it unites, no new head is regenerated, and regeneration is suppressed.

If one removes the crystalline lens in Triton, the upper edge of the iris regenerates a lens; if the iris is removed, the chorioid regenerates a lens; if the chorioid is removed, the retina forms a lens. Three different specialized tissues develop a lens under the influence of a purposeful organization. Any part of the Begonia plant reproduces the entire plant, and a severed leaf of the flowering plant proceeds at once to produce flowers. If a severed branch of the hydroid, *Antennularia,* is suspended in water, tip uppermost, twigs develop above, roots below, but if it is suspended tip downward, twigs replace the roots above and

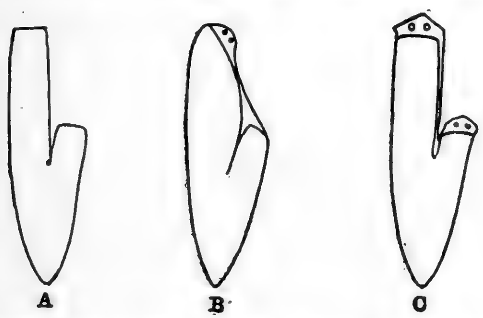


FIG. 15.—Regeneration in a planarian. *A*, lines of section; *B*, regeneration when divided ends coalesce; *C*, when divided ends are held apart (after Morgan).

roots the twigs below. This hydroid possesses a certain polarity of organization which is slowly alterable by gravity. Tissue cells also possess a polarity of organization, especially lining epithelial cells; and it would be an interesting study to trace the influence of disturbed polarity in the inception of tumor processes.

Throughout these and many other experiments in the mechanics of development it is evident that regeneration is controlled by the organization; and this, as Morgan [22] claims, can be defined only in terms of purpose, and cannot be wholly resolved into any known physical forces.

Now, a tumor can be defined only in terms of purpose. All the features of a malignant neoplasm are exhibited by the normal decidua, even to the destructive invasion of organs and cachexia; but the process is not a tumor, because of its purpose. Routine tumor diagnosis constantly involves the recognition of this fact, if errors are safely avoided. All of the above observations display, in clearer light, the meaning of the loss of organization in the regenerative processes in tumors. Yet experimental morphology has so far signally failed to elucidate the reason for the loss of organization in tumors. Much more definite results have followed from the study of cellular processes in development and regeneration.

The dividing embryo, up to the sixteen-cell stage, in some animals yields cells any one of which, if separated from the others, is capable of producing an entire embryo. Beyond this stage, and usually before it is reached, the cells become differentiated, different cell groups going to produce different specific tissues. According to Weigert[23] and Roux,[24] this differentiation results from an unequal division among the cells of the properties of the mother cells, eventually of the ovum, under the influence of an inherent internal impulse of the mother cell. Here again in the cellular processes of development is encountered the purposeful force of organization. As the tissues are differentiated in the embryo, owing to the unequal distribution of qualities or potencies, some cells come to possess more of one type and others more of another, while the sum total of the potencies of all types is necessary to maintain the equilibrium of the organization. Any alteration, as in the number of one type of cell, must necessarily affect all other types in the organization, if there is to be equilibrium. Hence, the cells, tissues, and organs stand in a relation of antagonism or correlation necessary to maintain the equilibrium of organization, any change in one affecting more or less all the others. This interdependence has been called by Hansemann the altruism of the cells. Removal of one kidney is followed by compensatory hypertrophy of the other through the physical factors of in-

Fig. 16.—*Achimenes Haageana.* A leaf-cutting of a plant in flower. The new plant, regenerating at base of leaf-stalk, proceeded at once to produce a flower (after Goebel).

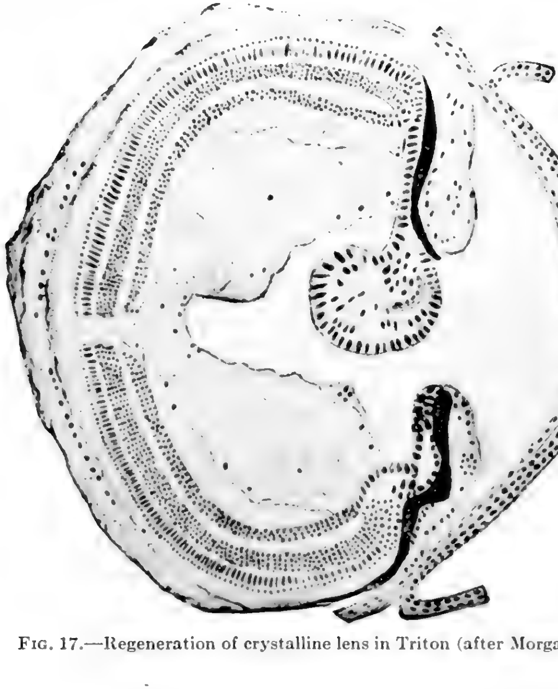


Fig. 17.—Regeneration of crystalline lens in Triton (after Morgan).

creased urea in the blood, increased blood supply, and nervous stimulus, all acting harmoniously under the influence of the organization. There is altruistic hypertrophy of many bones following destruction of the hypophysis in acromegaly, and altruistic atrophy of the adrenal in anencephalic monsters. A definite chemical substance conveying this altruistic influence may be found in the corpus luteum secretion which controls the growth of the chorion. The influence of the altruism of the tissues must be included in the conception of tissue tension.

Consideration of the internal processes in cell division also has important bearing on the question of organization and tumor growth. As long as the cells multiply by normal mitosis, and each stage of differentiation in one group is accompanied by equivalent antagonistic qualities in others, equilibrium is maintained. But if from the altered conditions occurring in inflammation chemical or mechanical factors derange the mitotic process, single chromosomes may be destroyed, the resulting cells will not receive the ancestral qualities in normal proportion, and a new biologic type will result which will not have the proper antagonists to balance it. Such cells will then be thrown out of the organization, and if their posterity suffer the same disturbance of the mitotic process they will eventually fail to receive any restraining influence whatever from the organization.

By such a process the theory of cell autonomy supposes that malignant tumor cells develop. But, before accepting any of these hypotheses, it must be demanded that tumors show some tangible evidence in support of them. Such evidence is by no means wanting.

The general history of malignant tumors is most consistent with the view that they represent aberrant tissues which have lost the control of the organization. Especially when the influence of all the factors in tissue tension which controls the growth of cells is considered, a moral certainty is established that the theory of cell autonomy is substantially correct and adequate.

The study of cell division under many conditions offers

strong support to the theory. Hertwig[25] has shown that by means of an external chemical stimulus by chloral hydrate a beginning mitosis may be suppressed and the nucleus return to the resting stage. When mitosis occurs later in such a cell it divides into four instead of two daughter cells. Hansemann's studies of tumor cells show that unequal, asymmetrical, and multipolar mitosis and destruction of chromosomes is of frequent occurrence, especially in the more malignant tumors. Hansemann[26] applies the term anaplasia to the condition of such cells; and these appearances may now be understood as signifying loss of normal differentiation, specific function, and organization. Anaplastic cells are, therefore, not embryonal cells, but a new type which have lost their place in the old organization. More or less anaplastic cells, with irregular mitosis, occur also in inflammatory processes, but this fact does not affect their significance in tumors. There are all grades of anaplasia as of malignancy of tumors: inflammatory hyperplasia passes gradually into neoplastic; and the fully anaplastic cell, capable of excessive growth, appears to be limited to malignant tumors.

In still another relation the study of cell division in tumors seems to have important bearing on the nature of the tumor process. In some animals the entire series of sexual cells, from the fertilized ovum up to the new egg cell, have been traced without a break. In this series the mitotic nucleus exhibits only one-half the number of chromosomes found in the somatic or general body cells, and these chromosomes, instead of assuming a V shape and radial arrangement, and splitting lengthwise in the monaster, are ring- or loop-shaped or composed of four coarse granules arranged in the long axis of the spindle. In higher animals the sexual cells are derived from the somatic cells by the gradual appearance of this type of mitosis, called "heterotype" or "gametogenous." These cells have very important altruistic relations in the organism, and in some insects their loss or the completion of their function entails death. Moreover, the sexual tissues may act as parasitic elements invading and destroying the somatic tissue, as in the embryo sac in

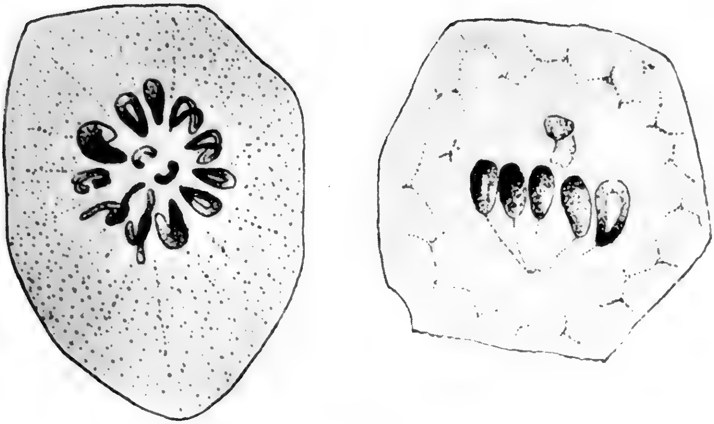


FIG. 18.—Heterotype mitosis in adenocarcinoma of trout (after Bashford).

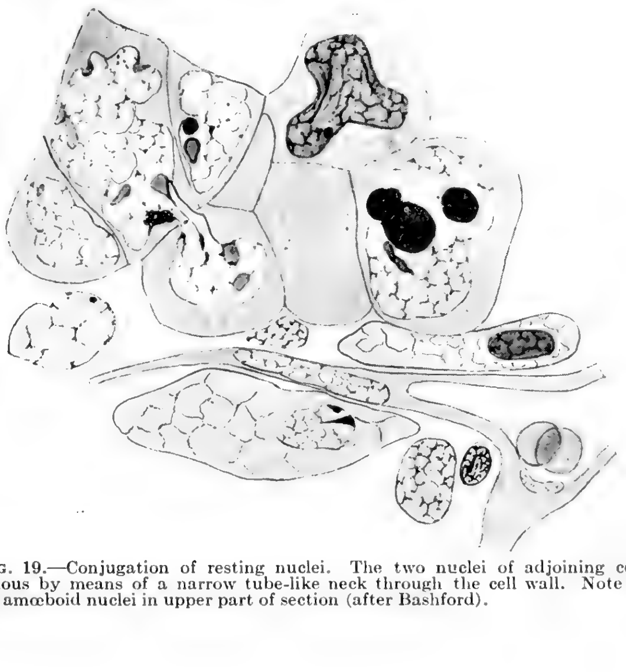


FIG. 19.—Conjugation of resting nuclei. The two nuclei of adjoining cells are continuous by means of a narrow tube-like neck through the cell wall. Note darkly stained amœboid nuclei in upper part of section (after Bashford).

the ovule of a flowering plant, or as the syncytial cells in man.

Recently Farmer, Moore, and Walker [27] have followed the development of heterotypic mitosis in the growing edges of epithelioma, and have found that this type of mitosis is common in this and other malignant tumors. Since tumor cells do not produce true sexual tissues, they apply the term gametoid to these mitoses in neoplasms. These observations support the view that tumor cells constitute a specific biologic series. Hansemann [28] claims priority in this conception, asserting that the same general ground is covered in his observations on mitosis in anaplastic cells. The two views have much in common and relate to identical objects; but Farmer, Moore, and Walker have taken one abnormal type of mitosis in tumors and attributed to it an entirely different significance from anything which I can find in Hansemann's interpretation.

The cause of gametoid mitosis is still to be determined. Chemical irritants are able to produce it in plants; and Farmer, Moore, and Walker attribute it to chronic irritation and other stimuli known to favor the development of tumors. Whatever its origin, observation teaches that it is chiefly found in anaplastic, lawlessly growing cells. Many criticisms of these hypotheses have succeeded in showing that tumor cells are not, because of their gametoid mitosis, equivalent to sexual cells; but they have not, I think, reduced the general significance of the fact that tumor cells and sexual cells now have three known common properties, heterotypic mitosis, destructive invasive properties, and striking altruistic relations.

The theory of cell autonomy claims, therefore, to have established the existence of a specific type of cell in malignant tumors, exhibiting the abnormal physiology and the peculiar morphology of anaplasia. The crucial question is whether the limitless power of growth of these cells has been explained satisfactorily. Ribbert emphatically insists that no unusual power of proliferation exists in cancer cells, that these cells freed from the restraints of tissue tension are merely exhibiting the powers of growth with which they are endowed from the ovum. He claims that there is no such thing as a malignant tumor cell

endowed with new and prodigious capacity for multiplication, but that tumor cells and their normal progenitors are alike in this respect. In this view he is supported by Weigert and Roux, who claim that the regenerative capacities of cells are determined from the moment of their derivation from the ovum and can never be increased by any external stimulus, although they are constantly restrained by the organization. In one sense, it is difficult to escape from the conclusions of Weigert and Roux, since it is the fertilization of the ovum which endows it with the particular organization and regenerative powers necessary to produce the adult organism, while fertilization of the new sexual cells is again necessary before new regenerative powers arise and produce a new organism. Recognition of this difficulty has led many to suppose that tumor cells are really fertilized cells, through conjugation with leucocytes (Klebs [29]), or by some form of parthenogenesis (Waldeyer [30]), or by conjugation of endothelium and fibroblasts (Recklinghausen [31]), or by nuclear conjugation of equivalent cells (Auerbach,[32] Bashford [33]), or by endogenous cell infection (Schleich [34]).

All observers have not accepted the Weigert-Roux hypothesis. Lubarsch finds it incompatible with the facts of metastases of malignant tumors, and claims that external stimuli may induce an enormous increase in the regenerative capacities of cells. It might be supposed that the excessive growth of tumor cells is merely an expression of an excess of regenerative power produced from the ovum as an increment of safety, in the sense of Meltzer.[35] But tumor growth far surpasses any limit of safety. Ehrlich [36] has computed the enormous bulk of mouse tumor which has been produced from cells of the Jensen strain, and it is conceivable that most of the earth's nitrogen might be converted into mouse tumor if only there were enough cancer laboratories. R. Hertwig,[37] J. Loeb,[38] Calkins,[39] Schucking,[40] and others have shown that the growth of cells, protozoon and metazoon, may be enormously increased by changes in the environment, and their observations as well as the history of tumor growth speak, in the judgment of many, against the Weigert-Roux theory.

The organized regenerative properties of tissue cells are truly determined in the fertilized ovum; but the mere *power of multiplication without organization* is subject to infinite variations from the influence of the environment, and, as has already been shown objectively, tumor cells may apparently grow forever.

We see, therefore, that the growth of tissue cells is normally controlled by the organization; that these cells possess regenerative powers greatly in excess of ordinary needs in order to meet extraordinary and accidental requirements; and that cells exhibit, in response to certain external conditions which some call stimuli, enormous grades of proliferative capacity. Why limitless growth should be such a striking characteristic of anaplastic cells which have lost the control of the organization we may not fully understand, but we can observe it as a fact.

The theory of cell autonomy, therefore, seems adequately to account for the phenomenal growth of tumors. It may be necessary to provide an external stimulus, but this necessity is not clearly apparent. So far as we know, the limitless capacity of tumor cells to absorb nutriment and grow may be an essential property of the protoplasm and organization of tumor cells, and beyond this descriptive knowledge we may not hope to penetrate.

Is the Parasitic Theory a Valid Possibility?—An important bearing of this discussion lies in the fact that it opens the way for the parasitic theory, which, according to the Weigert-Roux hypothesis, is not a valid possibility.

In the light of the facts illustrating cell autonomy, we may consider, finally, to what extent the action of parasites in tumors can be regarded as possible. Abandoning all claims to the demonstration of a cancer parasite, it is maintained that a parasite is the only form of external stimulus that can account for the growth of tumor cells. The question is a very narrow one and admits no obscurity. Can a parasite, growing with or within tumor cells, account for their lawless growth through endless generations, with the full preservation of their nutrition and vitality? It must be admitted that when the theory of

an external stimulus is allowed, the possibility that this stimulus comes from parasites is also accepted. That a cancer parasite is a logical possibility must be acknowledged freely. We cannot argue it out of existence from the nature of the tumor process. It may be shown, however, that it is unnecessary, unsupported by analogy, and inconsistent with the history of most tumors.

When one considers the importance of Cohnheim's discovery of the embryonal character of the cells of origin of many tumors, the evolutionary significance of neoplasms, the influence of specific substances presiding over nutrition and growth of many tissues, the general altruistic relations of cells and organs, the enormous regenerative capacities of mechanically-injured cells in man and lower animals, the conclusion slowly but inevitably results that the destructive growth of tumor cells is adequately explained by the theory of tissue tension and cell autonomy, and that a parasite is unnecessary.

When one starts out to find in nature an analogue for the cancer parasite which, instead of destroying its host, stimulates its nutrition and vitality, one fails to find any example of such a form of parasitism, and one must eventually subscribe to the second conclusion of Lubarsch that nowhere in the animal or vegetable kingdoms exists any analogy for the cancer parasite.

In many details the parasitic theory is inconsistent with the history of tumors and tumor metastases. For the extensive group of teratomata and of mixed tumors of organoid character it is definitely inapplicable, since these growths exhibit the natural development of embryonal tissues, and if this is parasitic, then, as Wilms [43] points out, the whole course of embryologic development must be of parasitic origin. In a metastasis from an ovarian teratoma Lubarsch [41] found brain tissue and ependyma in orderly arrangement. The atavistic nature of chorioma of the testis is unmistakable. Metastases are not always simple embolic groups of growing cells. Many of them are distinctly organoid in character, maintaining definite polarity in cell arrangement, and functionating as organs. Strictly comparable with the simple heterologous tumors are the aber-

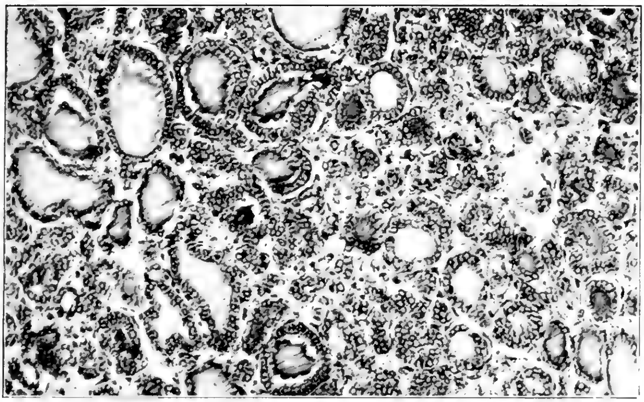


FIG. 20.—Adenoma of aberrant thyroid in dura mater. Case of Dr. F. M. Jeffries.

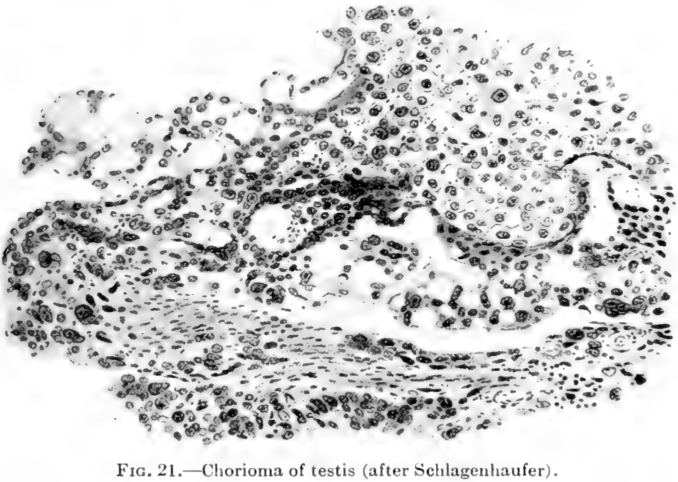


FIG. 21.—Chorioma of testis (after Schlagenhaufer).

rant adenomata of the thyroid, which Ribbert believes can only be explained as the result of emboli of normal thyroid cells.

Multiple enchondromata of the epiphyseal cartilages and along the vertebræ, which are imperfectly-suppressed remnants of an old chorda dorsalis, show distinctly hereditary features and cease to grow when the skeleton is fully developed. Lipoma passing into liposarcoma is often clearly connected with an obese habit of the individual. Moles and cutaneous angiomata are congenital in origin and remain harmless until mechanically disturbed. There are no essential differences among any of these tumors, since all occasionally produce metastases.

There remain for the possible application of the parasitic theory only the simple homologous tumors, including, however, the important group of cancers. Yet with the exception of the lymphosarcomata, whose position remains uncertain, the most minute study has failed to show any essential difference between the nature of cancer and that of the heterologous tumors.

Hopeless dilemmas seem to arise when one attempts to trace the necessary behavior of the cancer parasite. Some rare tumors, such as primary epithelioma or thyroid adenoma of bone-marrow and hypernephroma in distant organs, require that the parasite pick out minute aberrant groups of cells in protected situations. Chorio-epithelioma is one of the most characteristic and destructive of malignant homologous tumors. Its early phases, however, are with great difficulty distinguished from chorionic epithelium wandering within physiologic limits. It arises indifferently from uterine or tubal gestation or from hydatid mole. The adjacent maternal epithelium always escapes infection from any parasite in the fetal epithelium, although cancer of the uterus may arise during pregnancy. The various congenital sarcomata of the kidney very often develop *in utero* while the parents are free from demonstrable tumors.

Embryonal and misplaced tissue invaded by metastases fails to suffer infection. Hypernephroma frequently shows metastases in the healthy adrenal of the opposite side. Shaffer and Lubarsch [41] have described misplaced islands of gastric mucosa

in the œsophagus invaded by epithelioma of the œsophagus, but showing no hyperplasia. Berent[42] has observed a misplaced adrenal in the kidney containing a metastatic nodule from epithelioma of the jaw, but without showing any evidence of proliferation. A bruised pigmented mole may produce widespread metastases in a few weeks, or ten years may elapse after the removal of the melanoma before the appearance of rapidly-growing metastases.

The cancer parasite, therefore, must invade minute groups of cells in protected organs, even in the embryo of an immune parent; it invades only the tumor cells and their derivatives, but not other tissue cells; infecting one embryonal cell, it will not attack other embryonal cells in immediate contact; it induces destructive growth, ending in necrosis and fatal cachexia, or stimulates normal embryologic development with the production of comparatively typical tissues and organs; and it does all this with frightful rapidity in a few weeks, or it lies for ten years giving no hint of its presence.

The whole basis, objective and theoretical, of the cancer parasite has been traversed again and again, with the uniform conclusion by those who finish the journey that the cancer parasite is the cancer cell. We should, therefore, avoid the temptation of searching for an easy solution of the cancer problem and content ourselves with the more laborious but safer progress along the lines converging in the doctrine of cell autonomy.

III. BIOLOGIC AND BIOCHEMIC STUDY OF TUMORS.

During the past five years a new era in cancer research has opened in the study of transplanted tumors in lower animals. The results already obtained in this field are of such fundamental importance as to lead some to express the belief that the beginning of the end of the cancer problem is in sight. However enthusiastic such a hope may be, the most conservative estimate must acknowledge that the opportunity to study cancer under definite experimental conditions has placed the whole subject on a much firmer basis than has ever before existed.

The first definite success in the effort to transplant tumors from one lower animal to another appears to have been that of Novinsky,[1] who, in 1870, transferred a nasal cancer of a dog to two of forty-two dogs inoculated. In 1889 Wehr[2] transferred a vaginal sarcoma among dogs. Hanau's report[3] in 1889 of the transplantation of a squamous-cell epithelioma of a rat by intraperitoneal inoculation, and its further transfer to a third rat, was the first to receive general credence. In 1889 Morau injected an emulsion of a cylindrical-cell carcinoma of a mouse into ten other mice, and four weeks later found definite tumors of the same structure in eight of them.

During the following years he carried this tumor through seventeen generations and published the results in 1894.[4] He noted that the tumors remained stationary during gestation and that the offspring of tumor animals developed unusually large tumors.

In 1898 Velich[5] carried a sarcoma found in a rat through nine generations in rats, but he interpreted the results as a transfer of micro-organisms and not as a transplantation of tumor cells. In 1901 L. Loeb demonstrated before the American Society of Pathologists and Bacteriologists a transplanted spindle-cell sarcoma in a rat under such conditions as to leave little doubt of its genuineness. This tumor was later transferred through about forty generations, becoming increasingly infected with bacteria. From a cystic adenocarcinosarcoma of the thyroid in another rat Loeb[6] succeeded in growing seven generations of tumors, and Herzog[7] carried similar tumors through eight generations.

In Loeb's experiments there were several observations of importance. From the mixed tumor of the thyroid only the sarcomatous portion grew in the transplants, the carcinomatous parts being suppressed. Microscopical examination showed that the tumor grew from the peripheral cells of the transplanted piece. Tumor juice passed through filter paper proved ineffective. Pieces of tumor kept on ice five days were still viable. Tumors heated to 43° C. were markedly weakened in growth, beginning to grow later than the controls, growing more slowly

and regressing after five to eight weeks. Exposures to KCN, 1:700, for forty hours had the same effect as heating to 43° C. Pregnancy seemed to exert a favorable influence on the growth of the tumors. Transplanted pieces often grew more rapidly than the original tumor; but Loeb was unable to demonstrate an increase of virulence in the course of transplantation, believing that local conditions in the tumor tissue and in the inoculated animal had much to do with the rapidity of growth. Even more important was the demonstration of the value of the experimental method in the study of the general problems of tumor growth.

About this time Jensen [8] was carrying on a systematic study of a transplantable carcinoma in white mice from which reports were given during 1901 to 1903. The original tumor was a subcutaneous growth of the type of large alveolar carcinoma derived from the breast. The lymph-nodes were not involved. Portions of this tumor, or its derivatives, extending over nineteen generations, were transferred to 844 mice, of which 232 died within two weeks. Of 274 mice which received subcutaneous injections of comminuted masses of the tumor 121 developed tumors, and of 238 in which a small piece of tumor was inserted beneath the skin 28 developed tumors. The tumors grew from small peripheral islands of cells which survived the transfer. Small early tumors were less effective for inoculation than older ones, and Jensen concluded that actively mitotic cells were less resistant than older quiescent ones. Gray mice were more refractory than white mice, but when once transferred to a gray mouse the resulting strain proved equally virulent for both gray and white mice. Other varieties of mice, white rats, guinea-pigs, rabbits, etc., proved immune.

The "cancer parasites" were abundant in some tumors, absent in others, and cultures for bacteria and blastomycetes were negative. Complete comminution of the tumor cells or straining repeatedly through gauze removed the infectious agent from the tumor material. Kept at 37° C. for twenty-four hours, the tumor pieces lost virulence; but growth was readily obtained from pieces kept on ice for eighteen days. Exposure

for five minutes to 47° C. destroyed virulence, as did drying; but the cells resisted cooling to —18° C., which Folin has shown is the critical point for the vitality of frog's muscle. The failure of about 50 per cent. of the implantations to grow Jensen referred to slight family variations in the mice employed, but suggested that an abortive tumor might render the animal immune. He reported the cure of mouse carcinomata by means of the serum of a rabbit which had received injections of tumor cells.

Since the work of Loeb and Jensen the study of transplanted tumors in lower animals has been pursued energetically by Borrel in Paris, Ehrlich in Frankfort, Michaelis in Berlin, at the Gratwick Laboratory in Buffalo, by the British Commission in London, at the Rockefeller Institute, and elsewhere; and many new facts of great importance have been established.

Among these new facts may be mentioned, first, the demonstration that the inoculability of certain tumors among lower animals depends on the viability of the tumor cells; that the inoculation is a transplantation of the tumor and not an infection, since the new tumor grows from the transferred cells and not from the host's tissues. This fact has been shown for adenosarcoma of the thyroid in rats by Loeb, for the breast carcinoma in mice by Jensen, and for the lymphosarcoma of dogs by Beebe [9] and the writer. These results dispose of the supposition that the inoculability of these tumors favors the parasitic theory of their origin.

The demonstration of the extremely limited viability of tumor cells among the same or related animals is a very important result of the recent studies. Only in the mouse, rat, and dog have successful transplantations been secured. The British Commission made over 900 attempts to inoculate spontaneous tumors of horses, dogs, cats, and rats without a single success.[10] Ehrlich [11] reports only eleven transplantable tumors of ninety-four spontaneous growths observed in the Frankfort mice.

In rats, Hanau's epithelioma, Loeb's three growths of different structure, Michaelis's tumor, and that of Flexner and Jobling,[12] make six inoculable growths observed in this animal.

In dogs the lymphosarcoma of Wehr has been accepted by most observers as neoplasm; but with the excepton of Novinsky's somewhat uncertain case, this is the sole inoculable canine tumor.

The bearing of these results on the contagiousness of human cancer is obvious. Reviewing the proportion of successful implantations in animals of the same species, it appears that success with initial transplantations is the exception rather than the rule. Among 8000 inoculations of mice, with various mouse tumors, Bashford secured 1.5 to 50 per cent. of successes. Jensen obtained, through twenty-three generations, from 20 to 40 per cent. of successful inoculations, and Borrel about 10 per cent.

With rats a considerable number of animals has always been found immune; and the same rule holds with the lymphosarcoma of dogs, Sticker [13] recording numerous failures, and Beebe finding considerable difficulty in obtaining successful inoculations from primary growths.

It soon was apparent that tumors become increasingly virulent when repeatedly passed through mice of the same breed. The Jensen tumor, yielding 40 per cent. of successful inoculations in white Danish mice, was sent to London, Berlin, Paris, and Buffalo. Workers in each of these localities had some difficulty in keeping the strains alive, but by repeated inoculations successful results rapidly increased. Marked differences in susceptibility have been observed in the same locality between gray and white mice and between wild and tame mice of the same color. In fact, Haaland [14] has shown that Ehrlich's highly virulent sarcoma is virulent only for Berlin mice, but not for Danish mice; and that inbred animals are more susceptible to a tumor from the parents than are cross-bred animals. When the Berlin mice were housed and bred in Christiania they shortly became refractory to the Berlin (Ehrlich's) tumor. This remarkable transformation Haaland cautiously refers to change of diet. In Berlin the mice were fed chiefly on fat and animal proteid (milk), in Norway on carbohydrates.

These observations show that mouse tumor cells are ad-

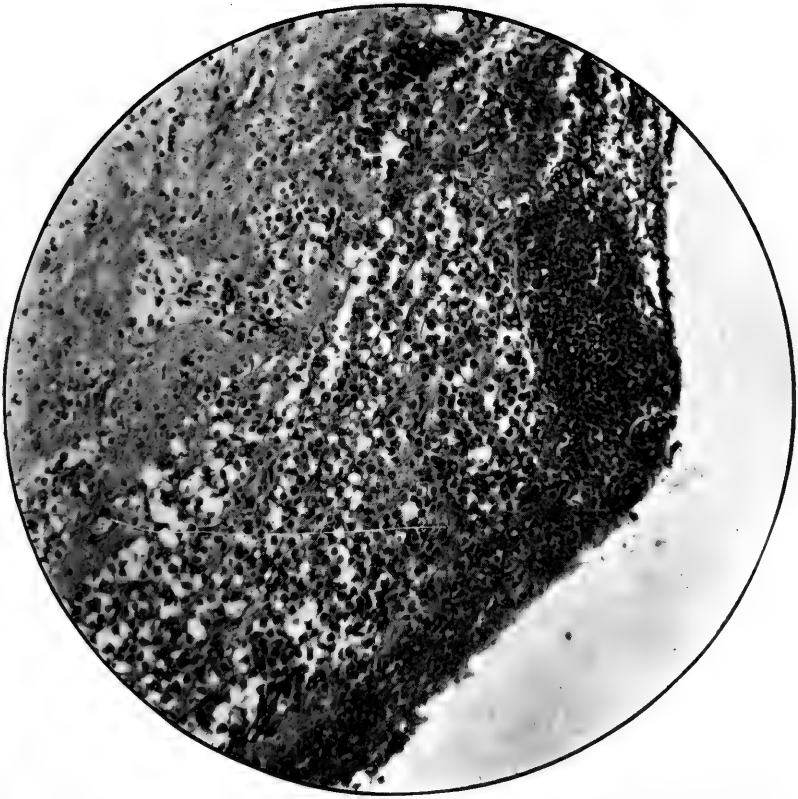


Fig. 22.—Lymphosarcoma of dog. Transplanted piece after twenty-four hours, showing zone of surviving cells. × 330.

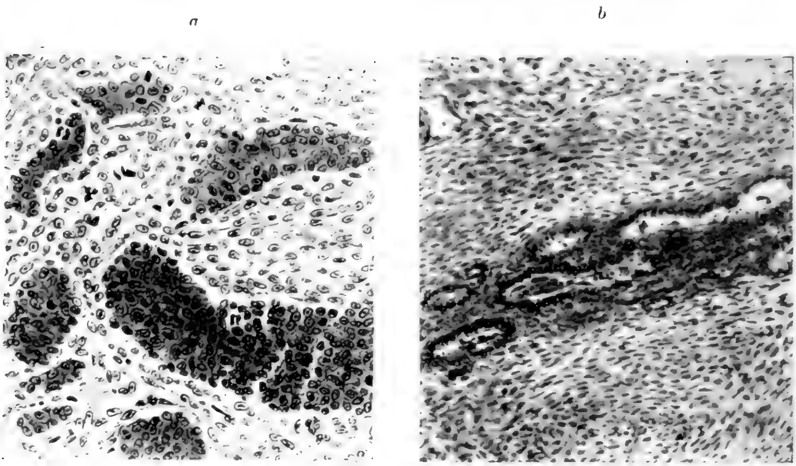


Fig. 23.—*a*, Mixed tumor of mouse (after Ehrlich). *b*, Human adamatinoma with fusiform epithelial cells resembling sarcoma.

justed with extreme delicacy to the nutrient soil, and that their growth or regression is determined by factors far more subtle than any heretofore demonstrated in immunity relations.

The study of transplanted tumors promises to throw light on some obscure phases of histogenesis in tumors. Loeb [6] observed that a diffuse spindle-cell sarcoma of a rat, when transplanted, assumed types of cellular arrangement designated as perithelioma (atypical), alveolar sarcoma or endothelioma, myxoma, and diffuse spindle-cell sarcoma. In a rat with a mixed adenocarcinosarcoma of the thyroid he found, in the lung, a pure sarcomatous metastasis; and on transplanting a portion of mixed tumor he observed only the sarcomatous elements in the secondary growth. The significance of this latter observation was elucidated more fully by Ehrlich,[11] who in the tenth generation of a carcinoma encountered a mixed sarcoma and carcinoma which by the thirteenth and fourteenth generations became a pure large spindle-cell sarcoma without carcinomatous elements, maintaining this character for at least fifty generations.

With another strain a similar transformation was observed, while a permanent mixed tumor was produced from the mixed material obtained from four strains, all of which were originally pure carcinoma. Apolant [15] and later Bashford [16] claim to have traced the development of the sarcoma from the stroma cells, although admitting the existence of cells which suggest a transformation of cancer into sarcoma cells.

Among human tumors the transformation of carcinoma into sarcoma is unknown. Metastatic melanoma of epithelial origin may, however, assume the characters of pure spindle-cell sarcoma. In adamantinoma the masses of enameloblasts which compose the tumor form areas of large spindle cells whose epithelial nature is proven by their formation of abortive enamel. In human tumors, therefore, the presence of spindle cells is not a sufficient indication that one is dealing with sarcoma; and further information about the spindle cells of mouse cancer is required before the exact significance of the transformation of carcinoma into sarcoma can be determined.

In transplanted mouse tumors, such spindle cells may be derived (1) from epithelium, (2) from the sarcomatous portion of a mixed tumor, (3) from the transplanted stroma, or (4) from the connective tissue of the host.

Working with mixed material of sarcoma and carcinoma it has been found possible to suppress, artificially, either element, since Haaland found Berlin mice susceptible only to the sarcoma, Danish mice only to the carcinoma, and Bashford believes he has hastened the transformation into sarcoma by immunization against the epithelial element.

The distinctions between benign expansive and malignant infiltrating growth are not rigidly maintained in experimental tumors of mice. The rate of growth of Jensen's cancer shows cyclic variations extending over periods of about 200 days (Bashford [17]). At the period of greatest growth it develops expansively and produces metastases without infiltrating tissues. Intraperitoneal implantation and advanced metastases of the same tumor, however, infiltrate neighboring organs; but when the infiltrating tumor is replanted subcutaneously the growth is again expansive. These distinctions, so important for the host, are, therefore, more or less accidental for the tumor. The occurrence of spontaneous variations in structure of the same tumor, transplanted in susceptible animals, may be kept in mind in considering Apolant's report [18] that by transplanting solid carcinoma in actively immunized mice he was able, in three instances, to transform the carcinoma into a benign adenoma.

In the transplanted tumor graft the specific cells multiply, but the stroma perishes and a new stroma is provided by the host's tissues. A possible exception to the rule is found in the transformation of carcinoma into sarcoma, reported by Ehrlich and Bashford, which they interpret as a neoplastic process becoming established in the host's connective tissues. In the lymphosarcoma of dogs we [9] have described the appropriation of some of the small transplanted blood-vessels by the new growing tumor. In metastases of mouse carcinoma the invaded tissues supply stroma, but are, as a rule, otherwise passive.

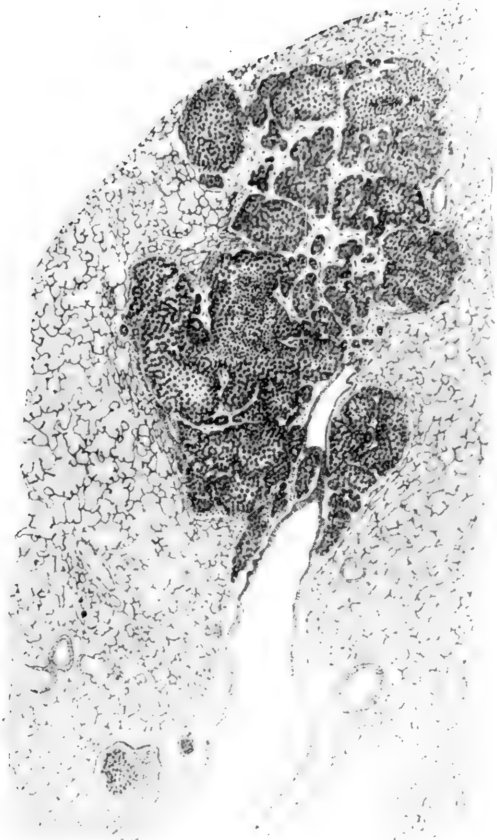


Fig. 24.—Transplanted carcinoma of mouse. Infiltrative and expansive growth of metastases in lung twenty-six days after intraperitoneal implantation (after Bashford).

Haaland, however, described the transformation of pulmonary epithelium into tumor cells in metastases of mouse carcinoma.

This interpretation of Haaland has not been confirmed and will doubtless meet with energetic opposition. Such a process is not recognized in human tumors; but, notwithstanding the determined position of Ribbert and Borrmann,[20] based chiefly on the study of gastric cancer and superficial epitheliomata, many (Virchow,[21] Hauser[22]) believe that there may be a gradual extension of the originating focus of a tumor. In primary adenocarcinoma of the intestine, and in melanoma, I believe that there may be a gradual transformation of normal epithelium into tumor cells.

Ribbert[23] has lately modified his former rigid position on this important question by admitting that cancers may arise from several foci, some of which appear later than others, and that there may be a gradual fusion of the tumors growing from these foci. It is obvious, however, that the distinction between primary tumors arising successively from adjoining foci and the gradual extension of a tumor process through normal cells is a matter of two interpretations of the same appearances.

Immunity.—Evidences of a peculiar type of immunity have from the first appeared in the observations on experimental tumors. Wehr[2] in 1883 described the spontaneous regression of the lymphosarcoma of dogs, a fact repeatedly verified for the same tumor by Sticker and Beebe. Loeb noted the complete absorption of many of his transplanted sarcomata in rats. Gaylord and Clowes[24] reported 20 per cent. of spontaneous cures of the Jensen mouse tumor, and they first drew attention to the significance of this fact as an indication of acquired immunity. The exact meaning is, however, obscured by the fact that some tumors regress while others grow in the same animal, and some after regressing for a time recover and go on to a fatal termination. A slight deterioration in the general health of the animal may interrupt the regression.

That local factors play a part in the limitation of the growths is indicated by the histologic study of regressing tumors. Such tumors are usually surrounded by a connective-

tissue capsule which invades the cellular edges, blocks the blood-vessels, which are often sheathed with round cells, and cuts off the nutrition. In regressing dog tumors we find fatty degeneration, transformation of large lymphocytes into small, compression atrophy at the periphery, and foci of liquefaction necrosis in the centre, mingled with areas of actively multiplying cells. If no other factor than anæmia were present these would be the logical changes. Loeb [6] found that if a regressing tumor were subdivided and replanted in the same animal it would often begin to grow rapidly. This observation is not in accord with the view that specific immune substances are present in the blood of animals recovering from tumors.

In July, 1905, Gaylord and Clowes [24] reported that thirty mice which had spontaneously recovered from definite tumors had proven immune to further inoculation with the same tumor, and that ten had resisted a third inoculation with a more virulent tumor. There were thus indicated: (1) The existence of acquired immunity against mouse cancer, (2) the possibility of increasing this immunity by a process of vaccination. In later experiments they were able to reduce the proportion of successful implantations of the Jensen tumor from 30 to 50 per cent. in the first series, to 10 per cent. for the second series, and to complete immunity in all surviving animals to the third inoculation. Yet, by vaccination with the Jensen tumor, they could not fully protect against the highly malignant Brooklyn cancer. Ehrlich,[25] by employing a hemorrhagic tumor which produced small abortive growths or none, was able to protect against tumors of maximum virulence. By repeatedly inoculating either the mouse sarcoma or the carcinoma he was able to protect against both sarcoma and carcinoma, and to a less extent against a chondroma, whence he concluded that the resistance established constituted a sort of pan-immunity against tumors. Bashford also obtained a high proportion of immune mice after spontaneous cure of tumors, and to a less extent after a negative inoculation of cancer tissue, which was promptly absorbed.

On the other hand, Haaland,[14] by inoculation of Jensen's

tumor, could not immunize Berlin mice against Ehrlich's very virulent sarcoma; and Michaelis [27] could not immunize white mice by means of cancers from gray mice, nor Berlin mice by tumors from animals bred in Copenhagen. It is possible that differences in technic and in the tumors employed may explain these conflicting results. At any rate, the large number of observations recorded show that a certain type of resistance against cancer has been produced in mice.

That a true specific immunity against tumors has been demonstrated beyond question cannot at present be claimed, for there are many disturbing factors which must be considered in the interpretation of the results of vaccination. The methods employed involve a process of elimination of weaker animals, which succumb to the treatment, and some of the animals which appear to have been rendered immune by the vaccination may always have been naturally immune to all the tumors employed, and this source of error can hardly be eliminated from statistical studies in which the condition of individual animals is not fully determined. Or non-specific variations in the general health of the animals may determine the result in mice, as it often does in dogs, and this factor cannot be estimated accurately in such small animals as mice.

Again, Bashford [17] has shown that different portions of the same tumor, and the same tumor at different periods of growth, vary in rate of growth, and that highly virulent strains may suddenly decline in virulence; but most of the experiments in immunization depend for validity on the assumption of uniform virulence of the tumor strains. Much depends on the dosage employed to test immunity. Successful results may follow multiple inoculations when a single implantation is negative; and Michaelis has seen a mouse, inoculated three times without result, take the fourth inoculation.

Finally, the artificial resistance against tumors does not appear to be specific. The pan-immunity observed by Ehrlich is a suspicious feature, suggesting the action of unknown and complex factors. Michaelis,[27] by the injection of normal mouse liver, was able to secure considerable immunity against tumors.

Schöne,[28] with the liver of mouse embryos and normal mice; Borrel and Bridré,[29] with liver or spleen; and Bashford,[30] with mouse red cells, all succeeded in rendering mice quite refractory to the growth of cancer cells. Bashford found that mice convalescent from infectious diseases were refractory to tumor cells, and he and Tyzzer [31] record the very interesting observation of the spontaneous development of cancer in mice which resisted inoculation. Lately [30] he reports that of all embryonal organs, inoculation by epithelial tissue gives the highest degree of immunity against cancer. Pregnancy retards the growth of mouse tumors and renders the animal less susceptible to inoculation. Reference may again be made to the remarkable results of increase in resistance observed by Haaland in Berlin mice transferred to Christiania, and probably due to change of diet, water and climate.

All of these considerations show that resistance of mice to tumors is of exceedingly complex nature and probably not comparable to any known form of immunity.

Not only may mice be made resistant to tumors, but their natural resistance may be diminished. In dogs there is a close relation between the general health of the animal and their susceptibility to inoculation with, and the rapidity of growth of lymphosarcoma, while inoculation with the filtered products of this tumor increases their susceptibility. Clowes [26] and Baeslack found that mouse tumors heated to 42° C. were more readily inoculable. This result is probably due to the greater proportion of autolytic products in the heated material. This same explanation probably applies to the results of Flexner and Jobling,[32] who rendered rats more susceptible to their tumor by injections of heated tumor products. They made the additional observation that the animals were especially susceptible, not immediately, but from the tenth to the thirteenth days after receiving the tumor products, suggesting a form of anaphylaxis. In the same line Borrel [33] suggests that perhaps mice may be made more susceptible to cancer by a diet of cancer tissue. It is known that the repeated injection of toxic proteids, both of bacteria and of organ cells, produces not immunity but in-

creased susceptibility; and there seems to be no reason why this susceptibility may not have the characters of anaphylaxis; but that it does has not yet been proven.

The effort to determine the nature of the immune forces against cancer has led to the formation of theories which have required frequent readjustment. It was natural to suppose that the blood serum of immune animals must contain substances directly antagonistic to tumor cells. This belief led Gaylord, Clowes and Baeslack [34] to inject tumor mice with the serum of recovered animals. Their first results were highly encouraging, since a minute quantity, 2 c.c., seemed to cause the rapid disappearance of some large tumors, while normal serum was entirely ineffective. These results, however, were not constant. They then mixed tumor emulsion with immune serum before injection, using salt solution and normal serum as controls, and found that the immune serum mixture gave 12 per cent. of successful inoculations, as compared with 31 per cent. for the controls. These results also are of uncertain value on account of many disturbing factors, but they indicate a cytotoxic action of the immune serum.

It first appeared that the active growth of a tumor was necessary to confer immunity; but Bashford [30] concluded that while the resistance established by a growing tumor is greater than that following an abortive inoculation, there is no relation between the grade of resistance established and the energy of growth or virulence of the tumor inoculated, but the protection is proportional to the quantity of tumor absorbed. In this case immunity must, apparently, depend on antagonistic substances produced in the body against tumor proteids. Yet, in the serum of actively-immunized mice, Michaelis [27] failed to find any evidence of cytolytic or agglutinative action on the tumor cells, or of complement fixation by the Bordet-Gengou method. Tumor cells treated with immune serum, with normal rabbit serum, with rabbit serum rendered hæmolytic to mouse red cells, and with serum of animals receiving injections of killed mouse tumor, grew quite as well as the controls. Borrel [33] failed to find any immunizing or curative influence in the

serum of a sheep receiving thirteen injections of 100 Gm. each of mouse cancer. As yet there has been no satisfactory evidence of the existence in the serum of immune animals of substances directly antagonistic to tumor cells.

Beebe and Crile,[35] after exsanguinating dogs suffering from advanced lymphosarcoma, have directly transfused them with large quantities of the blood of naturally immune or recovered animals. The result in nine cases was a rapid and complete disappearance of the tumors. This bold experiment would seem fully calculated to demonstrate in immune blood the presence of substances antagonistic to these tumor cells. Yet it is quite legitimate to suppose that the transferred immune blood was a more suitable nutriment for the body cells, and that as a result of the transfusion the balance of nutrition was reversed, the metabolism of the healthy tissues was improved, while that of the tumor was relatively depressed by the withdrawal of nutriment to such an extent that it underwent simple atrophy.

Athrepsia.—The observations on the viability of tumor cells in related animals has, from the first, suggested that the growth or regression of a tumor is determined by very slight variations in the soil, and that the problem of immunity is here one of the nutrition of the tumor cells. Ehrlich is the legitimate spokesman in this field, and he has designated [11, 36] this form of immunity as "athreptic." Transplanting mouse carcinoma into rats, he observed that the plant grew for several days, as in the mouse, but thereafter regressed. If, after a sojourn in the rat, the piece was transferred back to the mouse, it grew with undiminished vigor, after which it was again susceptible of considerable growth in another rat, but not in the one first receiving it. This zigzag transplantation he maintained for several generations. From these observations he concluded that the mouse tumor carried over into the rat a specific substance, or "*X-stoff*," which enabled the tumor cells, for a time, to absorb nutriment from the rat, but on the consumption of which the tumor ceased to grow and required a renewal of the specific substance in the mouse. Since a rat once serving as temporary host for the mouse tumor became thereafter entirely refractory

to the growth and could not serve a second time, it appeared that the tumor must soon absorb the limited supply of suitable nutriment in the rat or else that the rat once inoculated developed antibodies against the mouse cells.

Two forms of athreptic immunity are, therefore, possible. In one the specific substance is not itself the nutrient molecule, but merely facilitates absorption, although it is slowly consumed in the process. This theory finds an analogy in the relation of corpus luteum secretion to the chorionic epithelium. In the other view the specific substance is the nutrient molecule and is consumed in the growth. To what extent these hypotheses will prove adequate to explain immunity in tumors it remains for the future to decide.

That mouse tumors transplanted into rats fail to grow is doubtless due, to some extent, to the unfavorable soil. Here the influence of athrepsia seems obvious. But the fate of mouse tumor in rats recalls the experiment of Cohnheim and Maas,[37] who injected into the jugular vein of rabbits fragments of periosteum and saw them develop in the lung into islands of bone which grew for two or three weeks, but thereafter were absorbed. There is good reason to believe that these same islands of bone replaced beneath the periosteum would have retained their vitality. Here the influence of athrepsia is not so obvious, but other factors concerned in tissue organization seem to be at work.

It seems to be a fact also that tumors often regress in inoculated animals in which the soil is fully capable of supporting the growth, as is shown by successful reinoculation, but in which other factors, some of them local, interfere with the growth and effect a cure. A study of the conditions under which tumors naturally develop and grow indicates that suitable soil is of vastly wider distribution than is the occurrence of tumors, and that the fate of man or animal suffering from a malignant tumor depends chiefly on the characters of the cells and not on the soil. Outside of the experimental laboratory the soil seems to bear much the same relation to appropriate tumor cells as it does to the tubercle bacillus.

It might be supposed that tumor cells grow, not because they possess increased avidity for nutriment, but because the general body cells are deficient in this function. Yet tumor cells grow rapidly in young animals which show no such constitutional basis for the growth of tumors.

Chemistry of Tumors.—The chemical study of tumors forms a necessary preliminary to the construction of theories of immunity. If chemical or biochemical distinctions can be found between tumor cells and other tissues, then, and not till then, can a chemical or biochemical theory of immunity be established. Several interesting lines of research have extended into this field.

In rapidly-growing tumors, free from necrosis, Beebe [38] found an excess of potassium and a deficiency of calcium, while opposite conditions held in old and necrotic tumors. Clowes [39] observed the same relations in mouse tumors.

The proteids of tumors are said to differ in construction from those of normal tissues. On analysis, by Wolf,[40] cancer tissues yielded a high proportion (35 per cent.) of glutaminic acid; while alanin, phenylalanin, asparaginic acid, and diamino-acids were increased, and leucin diminished, in the results of Bergell and Dorpinghaus.[41] These results conflict with those of Petry,[42] Neuberg,[43] and Beebe.[44]

Nucleohiston is present only in lymph-nodes among normal tissues, and its appearance in cancers secondary in lymph-nodes suggests that metastatic tumors receive a chemical impress from the tissue in which they are growing (Beebe [44]).

Cellular tumors often appear to undergo autolysis more rapidly than many normal tissues, but it is doubtful if there is any normal tissue with which a comparison may properly be made. Petry[42] observed that antiseptic autodigestion of a breast cancer proceeded more rapidly, but in the same manner, as that of a normal breast tissue. Yet he is extensively quoted as having proven that tumors, in general, autolyze more rapidly than normal tissues. Comparing the increase in non-coagulable nitrogen in a carcinoma of the liver with that of the remaining liver tissue, during autolysis, Beebe [53] noted a considerable excess in favor of the tumor.

It is well known that tumors are very subject to softening and necrosis from infection and imperfect blood supply, but I do not think it has yet been proven that well-nourished tumor tissue undergoes autolysis more rapidly than an equivalent normal tissue. Beebe and the writer [45] passed dog blood by artificial circulation through test tubes containing fragments of dog sarcoma. Under these conditions the sarcoma cells remained alive for eight or ten days, but dog liver and kidney cells became necrotic and autolyzed extensively in forty-eight hours.

The study of special ferments in tumors was introduced by Buxton,[46] who, with Shaffer,[47] found no distinct differences in quantity or quality from those of normal organs. Harden and McFayden [48] found in tumors proteolytic ferments acting in acid and alkaline media, respectively, thus disproving Beard's supposition that proteolysis of tumor ferments is exclusively acid. A strongly hæmolytic activity of extracts of degenerating, and especially of necrosing tumors, has been demonstrated by Weil [49] as a factor in tumor cachexia, but this action is not specific.

Petry [50] found that the injections of extracts of fresh or of autolyzed cancers failed to disturb the nitrogen elimination in dogs, and he doubted if any of the cancer extracts were really active in the living body.

Blumenthal and Wolf [51] submitted five cancers to acid peptic and alkaline tryptic digestion. Two of them resisted pepsin, but three were digested readily in it, while all five were readily digested by trypsin. Yet they state that resistance to peptic and susceptibility to tryptic digestion is characteristic of cancer. Their results probably depended on a high proportion of nucleoproteids in some of the tumors and not on any significant peculiarity of tumor proteids. In two trials emulsion of cancer tissue not only dissolved itself but hastened the autolysis of liver pulp, whence they conclude that tumor ferments are not merely autolytic, as are those of normal tissues, but heterolytic. From these observations, which Neuberg [52] endorses, Blumenthal does not hesitate to draw far-reaching conclusions regarding the action of ferments in tumors, claiming that their infiltrative

growth and the cachexia which they produce are dependent entirely on the above characters of their ferments. The possible presence of bacteria, accidental necroses, and post-mortem decomposition in the tumors examined is not mentioned by these writers; and until their observations are reasonably controlled and greatly extended their conclusions cannot be trusted.

There are chemical problems in tumors, but the problem of tumors is not chemical. An experiment in antiseptic autolysis of comminuted cells, prolonged over several months, may be sound for chemistry, but is it fruitful for pathology? In these and other experiments the language employed and the conditions secured are those of chemistry, but the conclusions are drawn in a physiologic sense. Yet between the two there is a wide gap of assumption. The help of the chemists is needed, but until their technic approaches more closely to physiologic requirement it would seem that some of their results need not detain us long. The present studies do not, as a whole, offer a satisfactory demonstration that tumor cells possess chemical peculiarities sufficient to justify the assumption that they represent a specific biologic series.

In a biochemical sense the efforts to demonstrate specific qualities in tumor cells have not been fully successful. Mention has been made of Michaelis's failure to produce cytolytic, agglutinating, or precipitating agents specific for mouse tumor cells. Working with purified neucleoproteids, Beebe [53] has been somewhat more successful. From the nucleoproteids of a leukæmic spleen he produced a serum which agglutinated the emulsified cells of this spleen and also those of a lymphosarcoma, and precipitated the nucleoproteids from these sources, but acted very feebly and only in strong concentration on cells and nucleoproteids from normal spleen and other tissues, as well as from cancer and spindle-cell sarcoma. Similar results were obtained from nucleoproteids of cancer. If these indications prove trustworthy, then a biochemical basis for immunity against tumors may be within reach.

If any general criticism of the recent trend of cancer research is to be made it must apply to the exclusive relation of

these studies to the nature of the established tumor process and their failure to deal with the origin of tumors. These problems seem to be entirely distinct. Tumors grow readily in young dogs, rats and mice, although these young animals seldom or never develop such tumors spontaneously.

From this standpoint the more fundamental character and permanent value of the long line of studies on cell autonomy become conspicuous, for these deal with the origin of tumors. No one has yet succeeded in originating a malignant tumor experimentally, although the occasional effects of the X-ray may be so regarded. Very broad theoretic deductions have been drawn in the elaborate study by Von Dungern and Werner [54] regarding the response of epithelial cells to various stimuli. Fischer [55] has shown that extensive epithelial hyperplasia may be induced in the rabbit's ear by forcible injection of oil containing Sudan III, which seems to exert a peculiar attraction for certain epithelial cells of the skin. These observations may later be of value in the experimental production of tumors; but the essential character of a neoplasm, progressive growth, is so far lacking in the process excited by this method in the hands of many experimenters.[56] The long history of efforts to produce tumors experimentally indicates that many have been in control of single factors in tumor genesis, but no one has combined enough of these factors to secure the concrete result of a growing malignant neoplasm.

I am strongly of the opinion that information of fundamental importance in this field is still to be obtained by the very minute observation and analysis of the general and local conditions surrounding the early stages of cancer. This is the exclusive opportunity of the clinician, medical, surgical, and special, but it is often neglected. In it lies the chief hope, for the present generation, of a reduction in the mortality from cancer, by the earlier recognition of the precancerous stage of the disease and the elimination of some of its accessible factors.

The new era has not succeeded in devising a cure for cancer. While some are very confident, there does not seem to be

legitimate ground for hope that any will shortly be discovered. The chief definite limitation of the knife has come from a most unexpected quarter, in the form of the X-ray, which affects favorably only superficial tumors of moderate malignancy. Standardized *B. prodigiosus* toxins, as now used by Coley, are applicable only to a limited group of sarcomata. The X-ray, bacterial toxins, vaccination with *Micrococcus neoformans,* inoculation with the substance of thyroid, thymus, liver, and other toxic proteids, serum prepared against cancer tissue or its proteids, and Beard's pancreatin, all produce more or less destruction of the older portions of true cancers, with deceptive reduction in the size of the tumor, while the patient goes on to die from progressive infiltration by the more resistant tumor cells, and with accelerated metastases and cachexia.

The recent studies of artificial immunity to tumors in lower animals touch closely on the problem of the control of tumor growth in man, but the highly artificial conditions which form the basis of these experimental studies may cause disappointment when the attempt is made to transfer to man the results secured in lower animals. Yet the situation is encouraging in the present fixed determination to acquire more facts, in which field the experimental method is truly epoch-making; and cancer research may justly be stimulated, now more than ever before, by the reflection that a vast practical importance may at any moment attach to the new facts that are being gathered.

I. THE PARASITIC THEORY.

Most of the literature on Cancer is accessible in Wolff, Die Lehre von der Krebskrankheit, Jena, 1907.

[1] Loeb: Medicine, Detroit, 1900, vi, 286; Centralbl. f. Bakteriol. u. Parasitenk., Jena, Orig., 1904, xxxvii, 235.

[2] Borrel: Ann. de l'Inst. Pasteur, Par., 1903, xvii, 17.

[3] Gaylord: The Journal A. M. A., 1907, xlviii, 15.

[4] Plehne: Ztschr. f. Krebsforsch., Jena, 1904, iv, 525; Deutsche med. Wchnschr., 1906, xxxi, 1181.

[5] Pick: Berl. klin. Wchnschr., 1905, xlii, 1435–1440.

[6] Bonnet: Cit. by Pick.

[7] Riechelmann: Berl. klin. Wchnschr., 1902, xxxix, 728–758.

[8] Newsholme: Practitioner, Lond., 1899, lxii, 371.

[9] Haviland: Practitioner, Lond., 1899, lxii, 400.

[10] Behla: Deutsche med. Wchnschr., 1901, xxvi, 427.
[11] Arnaudet: Union méd., Par., 1889, xlvii, 613.
[12] D'Arcy Power: Practitioner, Lond., 1899, lxii, 418.
[13] Behla: Ztschr. f. Krebsforsch., Jena, 1907, v, 137.
[14] Sticker: Ztschr. f. Krebsforsch., Jena, 1907, v, 215.
[15] Prinzing: Ztschr. f. Krebsforsch., Jena, 1907, v, 224.
[16] Hahn: Berl. klin. Wchnschr., 1888, xxxv, 413.
[17] Cornil: Bull. Acad. de méd., Par., 3 s., 1891, xxv, 906.
[18] Hartmann (Lecene): Ann. de Gynéc. et d'Obst., Par., 1907, iv, 65.
[19] Butlin: Brit. M. J., Lond., 1907, ii, 255.
[20] Alibert: Cit. from Pianese ([26]).
[21] Washbourn (Smith): Edin. M. J., 1900, n. s., vii, 1.
[22] Park: Practitioner, Lond., 1899, lxii, 385.
[23] Lanz: Deutsche med. Wchnschr., 1891, xvii, 315.
[24] Demarquay: Cit. by Pianese ([26]).
[25] Guelliot: Union méd. du Nord-Est, Reims, 1891, xv, 33, 106, 135, 206, 306.
[26] Pianese: Beitr. z. path. Anat. u. z. allg. Path., Jena, I Suppl., 1896.
[27] Boinet: Compt. rend. Soc. de Biol., Par., 1894, 10 s., 11.
[28] Dagonet: Arch. de Méd. expér. et d'Anat. path., Par., 1904, xvi, 345.
[29] Leopold: Arch. f. Gynaek, 1900, lxi, 77.
[30] Jürgens: Verhandl. d. Berl. med. Gesellsch., 1895, xxvi, T. I., 99, 119, 152; Verhandl. d. deutsch. Gesellsch. f. Chir., Berl., 1896, xxv, T. I., 84; 1897, xxvi, T. I., 154.
[31] Werner and V. Dungern: Das Wesen der bösart. Geschwülste, Leipzig, 1907, 146.
[32] Grünbaum: J. Path. and Bacteriol., 1907, Edinb. and Lond., xii, 130.
[33] Leyden: Ztschr. f. Krebsforsch., Jena, 1904, i, 293.
[34] Borrel: Bull. de l'Inst. Pasteur, 1907, v, 497, 545, 593, 641.
[35] Rappin: Compt. rend. Soc. de Biol., 1887, 8 s., iv, 756.
[36] Scheurlen: Deutsche med. Wchnschr., 1887, xii, 1033.
[37] Francke: München. med. Wchnschr., 1888, xxxiv, 57.
[38] Lampiasi: Riforma med., 1888, Ann. iv, 20.
[39] Koubassoff: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1890, vii, 317.
[40] Doyen: Verh. d. deutsch. Gesellsch. f. Chir., Berl., 1902, xxxi, T. I., 68.
[41] Darier: Annal. de Dermat. et Syph., 1889, 2 s., x, 597.
[42] Albarran: Compt. rend. Soc. de Biol., Par., 1889, 9 s., T. I., 265.
[43] Thoma: Fortschr. d. Med., Berl., 1889, vii, 413.
[44] Sjobring: Fortschr. d. Med., Berl., 1890, viii, 529.
[45] Adamkiewicz: Untersuchungen über den Krebs und das Princip seiner Behandlung, Wien u. Leipzig, W. Braumüller, 1893.
[46] Soudakiewitsch: Ann. de l'Inst. Pasteur, Par., 1892, vi, 145.
[47] Monsarrat: Brit. M. J., 1904, i, 173.
[48] Foa: Gazz. med. di Torino, 1891, xlii; Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1892, xii, 185.

[49] Walker (Ruffer): J. Path. and Bacteriol., Edin. and Lond., 1892, i, 198.
[50] Sawtschenko: Centralbl. f. Bakteriol. u. Parasitenk., Jena, xii, 17.
[51] Pfeiffer: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1894, xiv, 118.
[52] Korotneff: Sporozoen als Krankheitserreger, 4°, Berlin, R. Friedländer & Sohn, 1893.
[53] Kurloff: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1894, xv, 341.
[54] Bosc: Compt. rend. Acad. d. Sc., Par., 1898, cxxvi, 541.
[55] Kahane: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1894, xv, 413.
[56] Eisen: Med. Rec., N. Y., 1900, lviii, 6.
[57] Schaudinn: Sitzunggeb. d. Berl. Acad. d. Wiss., 1896, xxxix, 951.
[58] Schüller: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1904, xxxvii, 547.
[59] Sanfelice: Ztschr. f. Hyg. u. Infectionskrankheit., Leipz., 1896–98, xxi, 32, 394; xxiii, 171; 1897, xxvi, 298; 1898, xxix, 463.
[60] Plimmer: Practitioner, Lond., 1899, lxii, 430.
[61] Leopold: Arch. f. Gynaek., Berl., 1900, lxi, 77.
[62] Roncali: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1895, xviii, 533.
[63] Bra: Le Cancer et son Parasite, Par., 1900; cf. Allg. med. Centr.-Ztg., Berl., 1900, lxix, 1137.
[64] Russell: Brit. M. J., Lond., 1890, ii, 1356.
[65] Schmidt: München. med. Wchnschr., 1906, liii, 162.
[66] Behla: Ztschr. f. Hyg. u. Infectionskrankheit., Leipz., 1899, xxxii, 123.
[67] Podwyssoski: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1900, xxvii, 97.
[68] Feinberg: Deutsche med. Wchnschr., 1902, xxviii, 43, 185.
[69] Gaylord: IV Report, Buffalo Cancer Laboratory, 1903.
[70] Robertson and Wade: Lancet, Lond., 1905, i, 218.
[71] Gaylord: J. Infect. Dis., Chicago, 1907, iv, 155.
[72] Calkins: J. Infect. Dis., Chicago, 1907, iv, 171.
[73] Robertson: Lancet, Lond., 1907, ii, 358.
[74] Virchow: Arch. f. path. Anat., etc., Berl., 1892, cxxvii, 188.
[75] Fox: Med. Chir. Tr., Lond., 1858, xli, 361.
[76] Klein: Beitr. z. path. Anat. u. Physiol., Jena, 1892, xi, 125.
[77] Lubarsch: Verhandl. d. naturf. Gesellsch. in Rostok, 1892.
[78] Darier: La Pratique dermat., Par., 1904, iv, 152.
[79] Stroebe: Centralbl. f. allg. Path. u. path. Anat., Jena, 1894, v, 11, 60, 105.
[80] Hertwig: Deutsche med. Wchnschr., 1902, xxvii, 221.
[81] Lubarsch: Path. Anat. u. Krebsforschung, Wiesbaden, J. Bergmann, 1902.
[82] V. Tubeuf: cit. by Lubarsch ([80]).
[83] Busse: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1894, xvi, 175.
[84] Rabinowitsch: Ztschr. f. Hyg. u. Infectionskr., Leipz., 1896, xxi, 11.
[85] Sternberg: Beitr. z. path. Anat. u. Physiol., Jena, 1899, xxv, 554, ibid., 1902, xxxii, 1.
[86] Richardson: J. Med. Research, Bost., 1900, v, 312.

[87] Nicolls: J. Med. Research, Bost., 1902, vii, 312.
[88] Mafucci: Ztschr. f. Hyg. u. Infectionskr., Leipz., 1898, xxvii, 1.
[89] Meser: Arch. f. path. Anat. (etc.), Berl., 1901, clxiii, 111.
[90] Borrel: Compt. rend. Soc. de Biol., Par., 1905, lix, 770.
[91] Wenyon: J. Hyg., Cambridge, 1906, vi, 580.
[92] Tyzzer: Soc. of Exper. Biol., N. Y., 1907, iv, 85.
[93] Mulzer (Hoffmann): Berl. klin. Wchnschr., 1905, xlii, 880.
[94] Löwenthal: Berl. klin. Wchnschr., 1906, xliii, 283.
[95] Guarnieri: Arch. per le Sc. Med., Torino, 1892, xxvi, 403.
[96] Bosc: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1903, Orig., xxxiv, 413, 517, 666.
[97] Michaelis: Ztschr. f. Krebsforsch., Jena, 1907, v, 189.
[98] Löwenthal: Deutsche med. Wchnschr., 1906, xxxii, 678.
[99] Halberstädter und Prowazek: Arbeit. a. d. k. Gsndhtsamte., Berl., 1907, xxvi, 43.
[100] Borrel: Compt. rend. Soc. de Biol., Par., 1904, lvii, 642.
[101] Lipschütz: Wien. klin. Wchnschr., 1907, xx, 253.
[102] Burnett: Ann. de l'Inst. Pasteur, Par., 1906, xx, 742.
[103] Borrel: Bull. de l'Inst. Pasteur, Par., 1907, v, 511.

II. THE THEORY OF CELL AUTONOMY.

[1] Remak: Arch. f. Anat., Physiol. u. wissensch. Med., Berl., 1852, xix, 217–57.
[2] Thiersch: Der Epithelialkrebs (etc.), 8°, Leipzig, W. Engelmann, 1865.
[3] Lobstein: cit. from Wolff, Die Lehre v. d. Krebskrankheit, Jena, 1907, 99.
[4] Waldeyer: Arch. f. path. Anat. (etc.), Berl., 1867, xli, 470.
[5] Durante: Arch. di Palasciano, 1874, 28, Maggio, cit. by Pianese.
[6] Cohnheim: Die progress. Ernährungsstörungen, in Vorlesungen über allg. Pathol., 8°, Berl., Hirschwald, 1877, vol. i.
[7] Critzmann: Le cancer, 12°, Paris, G. Masson, 1894.
[8] Beard: Berl. klin. Wchnschr., 1903, xl, 695.
[9] Bashford: Scientific Reports of the Imper. Cancer Research Fund, Lond., 1905, N. ii, Part II, 69.
[10] Ribbert: Beiträge z. Entstehung d. Geschwülste, Bonn, 1906, 1907.
[11] Borrmann: Ergebn. d. allg. Path. u. path. Anat. (etc.), Wiesbaden, 1900–01, vii, 833.
[12] Mayer: Ergebn. d. allg. Path. u. path. Anat. (etc.), Wiesbaden, 1903, ix, 518.
[13] Lubarsch: Die Metaplasiefrage u. ihre Bedeutung für die Geschwustlehre, in Arbeit. a. d. path. anat. Abteil. d. hyg. Inst. Posen, Wiesbaden, J. Bergmann, 1901, 205.
[14] Loeb: J. of Med. Research, Bost., 1901, vi, 44.
[15] Adami: Brit. M. J., Lond., 1901, i, 621.
[16] Oertel: N. York M. J., 1907, lxxxvi, 14.
[17] Benecke: Beitr. z. path. Anat. u. Physiol., Jena, 1891, ix, 440.
[18] Pick: Centralbl. f. Gynaek., Leipz., 1903, xxvii, 1033.

[19] Marchand: Ztschr. f. Geburtsh. u. Gynaek., Stuttg., 1895, xxxii, 405.
[20] Fraenkel: Arch. f. Gynaek., Berl., 1903, lxviii, 438.
[21] Patellani: Centralbl. f. Gynaek., Leipz., 1905, xxix, 388.
[22] Morgan, T. H.: Regeneration, New York, 1901, Macmillan Co.
[23] Weigert: Arch. f. path. Anat. (etc.), Berl., lxxxviii, 1882, 308.
[24] Roux: Arch. f. path. Anat. (etc.), Berl., 1888, lxiv, 113.
[25] Hertwig, O.: Die Zelle und die Gewebe (etc.), 8°, Jena, G. Fischer, 1893; see Benda: Ergebn. d. allg. Path. u. path. Anat. (etc.), Wiesb., I. Jahrg., ii, 541.
[26] Hansemann: Studien über die Specifität, den Altruismus und die Anaplasie der Zellen (etc.), 8°, Berlin, A. Hirschwald, 1893.
[27] Farmer, Moore, Walker: Proc. Roy. Soc., Lond., 1903, lxxii, 104; Brit. M. J., Lond., 1903, ii, 1664.
[28] Hansemann: Brit. M. J., Lond., 1904, i, 218.
[29] Klebs: Die allgemeine Pathologie (etc.), 8°, Jena, G. Fischer, 1887-89, t. ii, 399.
[30] Waldeyer: Deutsche med. Wchnschr., 1887, xxx, 925.
[31] Recklinghausen: Die Adenomyome des Uterus (etc.), Berlin, Hirschwald, 1896.
[32] Auerbach: Sitz. d. k. pr. Akad. d. Wissensch., 1891, 713.
[33] Bashford: Scientific Reports of the Imperial Cancer Research Fund, Lond., 1904, i. 16.
[34] Schleich: Deutsche med. Wchnschr., 1891, xvii, 83.
[35] Meltzer: Jour. A. M. A., Chicago, 1907, xlviii, 655.
[36] Ehrlich: Berl. klin. Wchnschr., 1905, xlii, 871.
[37] Hertwig, O. and R.: Untersuchungen z. Morphologie u. Physiologie der Zelle, 8°, Jena, G. Fischer; H. V.: Ueber den Befruchtungs und Teilungsvorgang (etc.), 1887. Hertwig, O.: Die Zelle und die Gewebe (etc.), Jena, G. Fischer, 1893.
[38] Loeb: Am. J. Physiol., Bost., 1901, iv, 452.
[39] Calkins: Arch. f. Protistenk., Jena, 1902, i, 355.
[40] Shucking: Arch. d. ges. Physiol., Bonn, 1903, xcvii, 58.
[41] Lubarsch: Path. Anat. u. Krebsforschung, Wiesbaden, J. Bergmann, 1902.
[42] Berent: Centralbl. f. allg. Path. u. path. Anat., Jena, 1902, xiii, 406.
[43] Wilms: Die Mischgeschwülste, Leipzig, 1900.

III. THE BIOLOGICAL AND BIOCHEMICAL STUDY OF TUMORS.

[1] Novinsky: Centralbl. f. d. med. Wissensch. Berl., 1876, xiv, 790.
[2] Wehr: Arch. f. klin. Chir., Berl., 1889, xxxix, 226.
[3] Hanau: Arch. f. klin. Chir., Berl., 1889, xxxix, 678.
[4] Morau: Arch. de Méd. expér. et d'Anat. path., Par., 1894, vi, 677.
[5] Velich: Wien. med. Bl., 1898, xxi, 711, 729.
[6] Loeb: J. Med. Research, Bost., 1901, vi, 28.
[7] Herzog: J. Med. Research, Bost., 1902, viii, 74.
[8] Jensen: Centralbl. f. Bakteriol. u. Parasitenk., Jena, 1903, xxxiv, 122.
[9] Beebe and Ewing: J. Med. Research, Bost., 1906, xv, 209.

[10] Bashford: Berl. klin. Wchnschr., 1905, xlii, 1433.
[11] Ehrlich: Arb. a. d. k. Inst. f. exper. Therap. zu Frankf. a/M, Jena, 1905, i, 77.
[12] Flexner and Jöbling: Jour. A. M. A., 1907, xlviii, 420.
[13] Sticker: Ztschr. f. Krebsforsch., Jena, 1904, i, 413; Arch. f. klin. Chir., Berl., 1906, lxxviii, 773.
[14] Haaland: Berl. klin. Wchnschr., 1907, xliv, 713.
[15] Apolant: Arb. a. d. k. Inst. f. exper. Therap. zu Frankf. a/M, Jena, 1906, ii, 48.
[16] Bashford: Berl. klin. Wchnschr., 1907, xliv, 1238.
[17] Bashford: Proc. Roy. Soc., Lond., 1906, lxxviii, 195; Scientific Reports of the Imperial Cancer Research Fund, Lond., 1905, No. 2, 52.
[18] Apolant: München. med. Wchnschr., 1907, liv, 1720.
[19] Haaland: Ann. de l'Inst. Pasteur, Par., 1905, xix, 165.
[20] Borrmann: Ztschr. f. Krebsforsch., Jena, 1904, ii, 1.
[21] Virchow: Die Cellularpathologie, 8°, Berl., A. Hirschfeld, 1858, 405.
[22] Hauser: Arch. f. path. Anat. (etc.), Berl., 1894, cxxxviii, 482; Beitr. z. path. Anat. u. Physiol., Jena, 1897, xxii, 587; Centralbl. f. allg. Path. u. path. Anat., Jena, 1898, ix, 221.
[23] Ribbert: Beitr. z. Ensteh. d. Geschwülste, II. Erg. Heft, Bonn, 1907.
[24] Gaylord and Clowes: Johns Hopkins Hosp. Bull., Balt., 1905, xvi, 130; Med. News, Phila., 1905, lxxxvii, 968.
[25] Ehrlich: Arb. a. d. k. Inst. f. exper. Therap. zu Frankf. a/M, 1906, H. II, 97.
[26] Clowes and Baeslack: J. Exper. M., N. Y., 1906, viii, 481.
[27] Michaelis: Deutsche med. Wchnschr., 1907, xxxiii, 826, 866; Ztschr. f. Krebsforsch., Jena, 1906, iv, 1.
[28] Schöne: München. med. Wchnschr., 1907, liv, 2517.
[29] Borrel and Bridré: Bull. de l'Inst. Pasteur, Par., 1907, v, 605.
[30] Bashford: Scientific Reports of the Imperial Cancer Research Fund., Lond., 1907.
[31] Tyzzer: J. Med. Research, Bost., 1907, xvii, 155.
[32] Flexner and Jöbling: Proc. Soc. of Exper. Med. and Biol., 1907, iv, 156.
[33] Borrell: Bull. de l'Inst. Pasteur, Par., 1907, v, 600.
[34] Gaylord, Clowes, and Baeslack: Med. News, Phila., 1905, lxxxvi, 91.
[35] Beebe and Crile: Proc. of the Soc. for Exper. Biol. and Med., 1907, iv, 118.
[36] Apolant: Therap. der Gegenwart, Berl. and Wien, 1906, xlvii, 145.
[37] Cohnheim and Maas: Arch. f. path. Anat. (etc.), Berl., 1877, lxx, 161.
[38] Beebe: Am. J. Physiol., Bost., 1904, xii, 167.
[39] Clowes: Am. J. Physiol., Bost., 1905, xiv, 173.
[40] Wolff: Ztschr. f. Krebsforsch., Jena, 1905, iii, 95.
[41] Bergell and Dorpinghaus: Deutsche med. Wchnschr., 1905, xxxi, 1426.
[42] Petry: Beitr. z. chem. Physiol. u. Path., Brnschwg., 1902, ii, 94.

[43] Neuberg: Arb. a. ad. path. Inst. zu Berlin, Feier Johannes Orth, Berl., 1906, 593.
[44] Beebe: Am. J. Physiol., Bost., 1905, xiii, 341.
[45] Beebe and Ewing: Brit. M. J., Lond., 1906, ii, 1559.
[46] Buxton: J. Med. Research, Bost., 1903, ix, 356.
[47] Buxton and Shaffer: J. Med. Research, Bost., 1905, xiii, 543.
[48] Harden and McFadyen: Lancet, Lond., 1903, ii, 224.
[49] Weil: J. Med. Research, Bost., 1907, xvii, 287.
[50] Petry: Ztschr. f. physiol. Chem. Strassb., 1899, xxvii, 398; Beitr. z. chem. Physiol. u. Path., Brnschwg., 1902, ii, 95.
[51] Blumenthal and Wolff: Med. Klin., Berl., 1905, i, 364; Ergebn. d. exper. Path. u. Therap., 1907, i, 65.
[52] Neuberg: Berl. klin. Wchnschr., 1905, xlii, 1189.
[53] Beebe: Communicated.
[54] V. Dungern and Werner: Das Wesen der bösart. Geschwülste, Leipzig, 1907.
[55] Fischer: München. med. Wchnschr., 1906, liii, 2042.
[56] Helmholz: Johns Hopkins Hosp. Bull., Balt., 1907, xviii, 365.

THE BEARING OF METABOLISM STUDIES ON CLINICAL MEDICINE *

DAVID L. EDSALL, M.D.,
Assistant Professor of Medicine, University of Pennsylvania, Philadelphia.

IN a pursuit like the practice of medicine, in which we have two kinds of possible activities, one essentially very close to pure science, the other engrossing practical work, those engaged in the two fields are likely to draw somewhat apart. There is a strong tendency for many of those occupied with scientific matters to keep their minds so closely fixed on the abstract problems they are endeavoring to solve that they forget to reconnoitre as they go along, and to attempt to determine—and they often forget particularly to point out—what practical bearings they may discover by the way. A certain number of such workers, indeed, frown very readily on frequent excursions into the practical application of science, as being somewhat cheap and likely to mix science and empiricism. They forget that in practical medicine we make such a mixture constantly, and must do so. Our efforts must be to avoid hasty and unreasonable application of science, but to apply whatever we reasonably can, provided we thereby do no harm, even though it be not completely demonstrated that our reasons for the practical measures are absolutely sound, for it is but rarely that absolutely final proof can be given. The clinician, on the other hand, finds it exceedingly difficult to keep up a serious acquaintance with scientific medicine. Consequently, he often feels unable to get for himself the practical bearings of scientific work that is of a kind outside of his own immediate interests, and, hence, tends to neglect these bearings more or less entirely; or sometimes he goes to the other extreme and draws those

* Lecture delivered November 30, 1907.

unjustifiably broad practical conclusions from scientific work that especially offend his more scientific brother.

So far as there is any fault in this, it must be divided. It is, indeed, scarcely the fault of either, so much as of the present-day demands on both. Nevertheless it is not unfair to ask, with Oliver Wendell Holmes, that the medical scientist shall serve his knowledge "with special limitations and constant reference to practical ends"; but at the same time to demand that those of us who are clinicians remember that not only must scientific knowledge accumulate, but its principles even more than its details need to be comprehended, if practical medicine is to be benefited by it. In one of the wisest and most charming of recent medical books ("Principia Therapeutica") Dr. Harrington Sainsbury says: "There are many who make light of general principles, knowledge of detail their sole demand; but this point of view sees one side only of the shield, be it silver or gold, as it shall please them; for while, doubtless, general principles without detail make but a foolish business, it is no less true that details without guiding principles yield but a busy foolishness." My warm sanction of this remark and my feeling that both clinicians and medical scientists often make too indifferent a search for the practical guiding principles that may be derived from exact investigations were, indeed, the things that determined me to treat my subject in a general way rather than by going into a detailed discussion of specific facts of the subject. Studies of metabolism, in the broader sense of this term, are, I think, a more fruitful source of clinical principles than is any other form of investigation, unless it be that relating to hygiene. The most direct reason for this is that they are carried out on living beings and deal with living processes while the latter are still in action. A more prosaic but still not inconsiderable further reason is that a large part of the conclusions are derived from actual figures, often, indeed, by balancing one column of figures against another. Figures are very convincing and clarifying to the human mind, and give much less opportunity to indulge any unconscious personal bias than does clinical observation, or even morphologic or most

other accurate studies into which figures do not enter, and it is in ridding him of bias that investigation is most useful to the clinician.

SCIENTIFIC AND LITERARY STYLE.

In his essay on "Style" Walter Pater describes the scientific style as presenting facts painstakingly as such, unembellished by imagination, while the literary style, "as it more closely approaches fine art," becomes more and more the presentation of facts, not simply as such and as accurate truths, but in the form of truths as they appear to the writer—"soul facts," as he calls them. Considering that he is working for the art of medicine as well as the science, I think the medical scientist often presents his facts too little embellished, but, on the other hand, being a clinician, I may say without impertinence that, surrounded as he is by impressive human happenings and a complexity of the details of disease, the clinician's tendency—a tendency that it is always his earnest desire to avoid—is frequently to make for himself "soul facts" that do not bear contrast with the real thing, if the latter can be found. Nothing, to my mind, succeeds better than a few figures in determining whether our conceptions are scientific or "fine art." These figures sometimes destroy idols and may leave nothing in place of them, but this is, at least, more satisfying than error. They often simply confirm vague beliefs or traditions that were based previously merely on observation, but this gives confidence in place of uncertainty. Frequently they yield new facts that could have been learned in no other manner.

Among the many ways in which metabolism studies have already influenced clinical medicine and will continue to do so, I have been particularly impressed with some of those that often escape notice, chiefly, I imagine, because they are so simple and elementary that serious students of the question scarcely think any more of many of them. Among the most prominent of these, to my mind, is the effect that such studies have quietly exerted on the clinical use of changes in excretion in reaching diagnostic and therapeutic conclusions. In this point more

than in any other, perhaps, there has been the tendency among clinicians to use details irrespective of the principles that govern these details. Some of the simplest principles of metabolism have often been overlooked, and, as a consequence, false diagnostic premises have often been built up. A correct appreciation of our knowledge of metabolism has served chiefly an iconoclastic end in this connection, but it is none the less serviceable; for no thinking person can doubt that to destroy a false belief is quite as useful as to demonstrate a new truth.

RELATION OF EXCRETION TO INGESTION.

The older literature was burdened with discussions of the value of things so inevitably unreliable as the determination of the percentage of urea, of uric acid, of various other excretory products, and of sugar, in a specimen of urine, without any consideration of the relation of this specimen to the total amount passed in the day. Such measures are, indeed, still carried out to some extent, as indications of the excretory capacity of the kidneys, of the kind and extent of any metabolic disorder that may be suspected, or as an indication of the severity of a glycosuria. It does not take a lively imagination to realize that variations must occur in accordance with the period of the day at which the specimen has been secured, but it has been necessary to accumulate demonstrative evidence of this to convince many minds; and some persons even yet remain so unfamiliar with the basic facts of excretion that they still fail to comprehend so simple a principle, and do not realize that first of all the mixed urine of a twenty-four hour period must be studied if one is to have the slightest idea even of the real amount of any substance that is being excreted.

So simple a fact as this is readily understood and comparatively little neglected now by careful clinicians; but, though it would seem to be equally true without demonstration, it takes much more emphatic evidence to convince most persons that the excretion of any substance varies with the amount taken in of the substance itself, or of the foods that yield it. It is fruitless to attempt to reach any accurate conclusions on the basis

of studies of excretion unless one knows the amount taken in of those substances that influence this excretion. There is a general comprehension of the fact that a glycosuria is largely influenced by the diet; the relation is, indeed, so direct that it is traditional lay knowledge. But this knowledge is even yet too infrequently considered in judging of the severity of a glycosuria, and it has taken a long time to convince many who have little interest in metabolism that estimations of urea mean nothing unless accurately contrasted with the amount being taken of urea-yielding foods. If those who in their studies of renal cases have made urea estimations—and especially our colleagues, the obstetricians, who have devoted much discussion to this method of diagnosis—had had the opportunity to see the nitrogen excretion in a normal person vary from a few grammes to thirty or more, in accordance with mere changes in diet, the time that they have lost over this point would have been saved. Accurate metabolism studies carried out chiefly by von Noorden and his students have, indeed, shown us how impossible it is, even in marked nephritis, to reach any certain diagnostic or prognostic conclusions from the most careful attempts to demonstrate retention, for retention is by no means the rule even in very bad cases, and it ordinarily varies with excessive excretion; and where retention occurs it may be due to poor excretion or to actual building up of tissue, the latter, of course, being usually a good omen rather than a bad one. A number of other factors, such as the absorption and excretion of œdema fluid, also influence results so largely that clinical deductions are usually unwarranted from such studies.

THE VALUE OF CRYOSCOPY.

This same point of view that I have just been discussing might have saved medical and surgical clinicians much useless labor in more recent years in other studies of the functional capacity of the kidneys. A very large part, for instance, of the work that has been done regarding the excretion of sodium chloride in renal disease has been carried out without any consideration of the diet, and all that work is, therefore, nearly

or quite worthless. In most of the work on cryoscopy also the diet has been neglected, and the results are, therefore, especially in cryoscopy of the urine, almost entirely valueless. Indeed, because things are excreted in different form from that in which they were ingested, we have no way of telling accurately what effect changes in diet would have on cryoscopy of the blood even, and especially on cryoscopy of the urine, except that we can test the influence of an absolutely exact standard diet in numerous different individuals, and can take an average of this and call it a normal. While the results would perhaps be reasonably accurate in normal persons, changes in metabolism as well as in excretion would largely affect the result, and we have no means in any cases under observation of telling whether the abnormalities are the consequence of metabolic or of excretory conditions. Therefore, a method that is in itself so exact as to fascinate the mind becomes clinically of little value in studying disorders of excretion, except in contrasting the concentration of the urine as secured separately from the two kidneys. Neglect of this view of the question has, it appears to me, led to a great deal of time being wasted in attempts to use this method for the elucidation of questions that it could not clear up.

Similar remarks apply to various similar studies and conclusions. Theories, and even descriptions of distinct diseases, have, for example, been built up on the mere presence of precipitates of oxalates and phosphates in the urine. There are some interesting questions, as yet not solved, regarding the relation of oxalates to digestive disturbance; and, to my mind, there is a much broader and more interesting relation than is usually admitted now-a-days between so-called oxaluria and metabolic disturbance.

I have seen some exceedingly curious examples of a close relationship between oxalate precipitates and clinical symptoms; such, for instance, as a mania of a few days' duration in the convalescence from an acute pneumonia, the urine containing oxalate crystals during the period of mental disturbance, but not before or after. The oxalate precipitates, I take it, are

merely an index that something else is going wrong; they are, of course, almost certainly not the evidence of oxalic-acid poisoning, and usually not evidence that the amount of oxalic acid in the urine is increased.

As to the phosphates, theorists have even gone so far as to describe distinct nervous disorders due to a loss of phosphates from the system, basing this almost solely on the presence of precipitates of phosphates in the urine. Real studies of metabolism have, of course, in most such cases, shown that there is no excess in the urine; that the phosphates precipitate because of conditions unfavorable to their solution, or if the amount happens to be large it is ordinarily because an excess has been taken in the diet. There are unquestionably peculiar and interesting problems to be worked out in connection with some of these cases of phosphate precipitates. In some instances they present almost a definite syndrome, particularly certain cases in which I have been much interested in which the urine periodically becomes alkaline, phosphates precipitate out, and this is soon followed by a migrainous headache, and subsequently by symptoms appearing to indicate that the individual is eliminating toxic material through vomiting, diarrhœa, or diuresis. The attack is then over. In some cases with phosphate precipitates I have found the rather curious condition of an excessive excretion of ammonia, without any apparent reason for it. Ordinarily excess in ammonia excretion means, of course, the presence of an undue amount of acid in the system, and the excess of ammonia is present in the urine simply because it has been used to neutralize the acids, but in these cases there is no evidence of acidosis. The conditions, indeed, are so far from it that the urine is alkaline when passed. What such conditions mean I do not know.

A similar instance of a hasty conclusion that was soon set right by real investigations of metabolism is the claim made a few years ago by some of the French school that pulmonary tuberculosis is associated with and more or less dependent on a "demineralization" of the tissues; that there is a regular loss of mineral salts from the tissues. This statement was soon

corrected by accurate metabolism studies by Ott and others, and it need never have been made had a proper contrast between intake and outgo been worked out in the beginning.

THE "URIC ACID DIATHESIS."

In no relation in the whole range of medicine has this point of view been so thoroughly obscured and so often lost sight of as in all the labor that has been expended on the building of idols of uric acid and in breaking these same idols afterward. A very large part of this labor might have been saved could both clinicians and physiologists have started with the same conception that we have long had regarding other excretory products, that is, that the excretion is largely influenced by the amount of uric-acid-yielding foods taken.

Whatever direct relation to the causation of disease uric acid may ultimately be shown to have,—and this, I think, will probably be slight,—we have, at least, learned that mere studies of its excretion are of little, if any, clinical value; first of all, because the amount excreted is, in large part, directly dependent on the kind of food taken, and, worse than this for the clinician, because a certain amount is formed in the organism, and not only directly from tissue breakdown, but also, almost certainly, synthetically. We do not know how much this is normally, and cannot tell at all, therefore, how much it may be in disease. To add to the complexity of the question, we have learned that some of that derived from the food, and some that is formed in the organism, is altered to other substances in its travels through the body, but we do not yet know how much, and we know almost nothing about the way in which some of these variable factors are influenced by most diseases.

We cannot, therefore, by the most exact methods of studying excretion tell more about uric acid or the total purin metabolism than that the amount of the various purins in the urine is larger or smaller than it should be on the diet then being used; and that this may be due to abnormalities of excretion or to disorders of oxidation, synthesis, or other metabolic processes. We

have no accurate scientific conception as to which is at fault in any particular instance.

When I was graduated in medicine, stress was still often laid on uric-acid precipitates as indicative of disease depending on uric acid. Yet it was apparent, even long before this time, that such precipitates mean of themselves nothing regarding the amount of uric acid in the urine, but are due to the effects of low temperature or chemical changes in the other components of the urine that affect the solubility of the uric acid. Traces of such elementary error in teaching, however, still remain in some medical writings that carry authority. When we learned laboriously the striking influence of diet on uric-acid excretion, the door appeared to be open to some definite knowledge; but the relative effects of abnormalities of synthesis, oxidation, and excretion cannot yet be reckoned with at all.

So far as I can see, of all the clinical uric-acid idols, at least of all those relating to the excretion of uric acid, but one remains—the recently determined fact that gouty persons excrete but a small amount of endogenous uric acid, and they excrete the uric acid derived from the food slowly or imperfectly, if one makes careful quantitative studies of the excretion over a period of many days. This idol, too, I strongly suspect, will in large part fall. The diagnostic, and to some extent at least the therapeutic, conclusions built on it will, in that case, fall with it. I have already observed cases other than gout in which the same thing occurs strikingly, and other persons have done the same. Probably this will prove to be frequently true, and the abnormality will be shown to be the result of so many causes that it can have no important significance in relation to gout from the diagnostic standpoint. Yet, though the status of the studies of the excretion of uric acid is what I have indicated, I am still frequently met with the request, from some of my most respected clinical associates, to point out to them how they can get help in their diagnoses by making studies of the amount of uric acid in the urine. It may be that better results will be obtained from studies of the exact amount in the blood, a method that has recently been systematically used for diag-

nostic purposes, but the value of such studies is not yet clear, for many of the above-mentioned objections apply to it also and it is too difficult for ordinary clinical purposes.

Such are examples of "soul facts" that have been demonstrated to be such through metabolism studies, and as a consequence of our better knowledge, the false diagnostic and therapeutic conclusions built on them have more or less completely disappeared. The influence of metabolism studies, however, has been by no means solely iconoclastic. Probably in no line of medical work have the methods followed been more purely empirical until recent years than those used in dietetics, and yet in scarcely another line of work has so much labor been expended in the last generation in accumulating facts. These facts are, however, only beginning to be widely appreciated. Dietetics is much less a matter of mere experience and personal opinion than it was. All humanity finds it much more difficult to make use of new knowledge and laws relating to the things that we have grown up with than in connection with matters that are themselves new and strange, and food is so old a story that it is difficult to teach ourselves to examine into its use in medical practice in much the same way that we study the use of other therapeutic measures.

DIETETICS.

In dietetics we remain much more prone than in most other medical practices to work with details, regardless of principles, instead of using whatever principles we have in leading us to correct details. Indeed, it appears to me that a writer to whose wisdom I have already emphatically referred comes very close himself to recommending in dietetics the "busy foolishness" that he so scorns in drug therapy, when he practically advises us not to bother our heads about the discussion of food standards, but to attend to the details that suit the individual.

We must always arrange our diet for individuals and not for a mere average human being. But in dealing with serious conditions by using drugs we are dependent, first, on knowledge of what the action of a drug really is, and, in the second

place, on knowledge of the dose that is usually effectual and safe. If we would be accurate in regard to the much more vital question of foods,—and particularly if we would be accurate in dangerous cases, in which we ourselves are largely responsible for the amount and character of the diet and in which, if any grave errors occur, we alone are at fault,—we must know, first of all, what the actual nutrient powers of the food we use are, and how much of it an average individual ought to have, if he is to be neither starved nor overburdened. It is quite true that the physiologist asks a little too much of us when he presents the matter to us, as he often does, in such a form that it would appear that to arrange a diet with reasonable accuracy is almost the same as to conduct a laborious physiologic experiment, and both the physiologist and the clinician discuss these standards too much as if they were absolute things, that are meant to be followed literally, instead of being simple guides; and yet at the same time that he demands absolute rules the clinician sees the impossibility of constant standards, for he knows that we deal with complexities of disease and temperament that make absolute accuracy a thing that even the physiologist cannot reach with his most exact methods, and that with patients who are not seriously ill it is utterly impossible in ordinary practice to be more than approximately accurate in attempting to make dietary regulations approach standards. Hence he often objects that these standards are worthless and makes no attempt to use them. But the clinician might remember that he does not demand absolute standards in other things, as, for instance, in the use of drugs. He makes allowance for temperament and for peculiarities of disease in such things, but in this present day he would be looked on as a dangerous character if he had not learned what the pharmacologist has taught us as to the effect of drugs and the amount that may wisely be used with the average individual.

If it were a general custom to look at foods, first of all, from the same point of view as drugs are looked at,—from a consideration of the kind and amount of their food value, on the one hand, and of the food demand of the average individual

of a given size, on the other,—we should less frequently see persons fed on a diet that may be big in bulk, to be sure, and that may look impressive on the records, but that is composed of material of so little food value that the whole amount evidently means a considerable degree of starvation when its caloric value is contrasted with the real demand. We should then less frequently see disease made more grave and convalescence more prolonged through the use of such a diet, and we should have been quicker to recognize, for example, that profound exhaustion, fever, delirium, and other symptoms in the later stages of acute disease and in the convalescence—particularly in typhoid fever—are the result of too limited a diet quite as frequently as they are due to continued toxæmia, a fact that is particularly true in dealing with children. On the other hand, we should see less enthusiasm over many of the so-called "free diets" used in typhoid fever during recent years, if we were accustomed to looking at a diet list in such a way that it becomes apparent that many of these free diets are, to be sure, more solid, but at the same time less nutritious, than is a reasonably generous milk diet.

Such methods can easily be used in severe disease, for, with a patient at rest, his food demand is apparent, and the diet is simple and its value easily determined. A little practice gets one into the habit of thinking in this way. When diets are more complex, we must trust chiefly to judgment, to the patient's appetite, and to observation of the effects, rather than to figures, in regulating the amount of food, but even here we can avoid such gross errors as burdening a delicate child with an amount of food that possesses two and a half times the amount of calories that an adult would need and wondering why his health does not improve—an example of what I have seen done. If, too, we followed some of the details of clinical studies of metabolism and absorption we should know, for instance, that over-generous feeding in conditions like pulmonary tuberculosis is not only evidently likely to tax digestion, metabolism, and excretion; it has also been shown often to result merely in burdening the digestive tract and in expulsion of much of the

food, especially much of the fat, in the fæces; so that the end-result is merely to overwork digestion and to waste food.

I can state without fear of contradiction that the number of clinicians that habitually use the available knowledge of dietary standards, food values, digestion, and absorption of foods, the behavior of foods in the course of metabolism, and the chief excretory products of food in helping them to plan their diets, is extremely small as compared with the number that employ whatever accurate knowledge we have in connection with the much less serious question of the use of drugs. I believe that quite as many patients are damaged by faulty use of foods as by faulty orders concerning drugs. Our knowledge of these various questions concerning dietetics is very imperfect in many particulars, but it is no more imperfect than is our knowledge of drugs and many other therapeutic measures.

SPECIFIC DIETS.

There are, it appears to me, two striking errors besides inexactness in the general view of dietetics—errors that our knowledge of metabolism can largely set straight at once. One is that often vague, but nevertheless common, feeling that the details of a diet should be specifically suited to the disease in which it is to be used. We have got well past the point where we thought drugs to be frequently specific in their action. We should make the same confession in regard to diet, and we should get farther. We know almost nothing about any actually specific alterations of general nutrition that may occur in specific disease, and we know comparatively little of the specific effects of different foodstuffs on normal nutrition.

To attempt to arrange actually specific diets is, therefore, in most diseases impossible and it is questionable whether we shall ever get to the point at which we can do this. Just as in the general treatment of particular diseases our measures are almost always directed not against the disease as such, but against certain conditions that occur in that disease (these conditions, however, usually occurring in many other diseases, in different combinations) so, in diet, do we study and treat,

not diseases, but conditions, such as overnutrition, undernutrition, irritability and sluggishness of the digestive tract, exalted and sluggish metabolism, and difficulties in excretion. Dietary studies have taught us how to meet with considerable exactness general excessive or reduced nutrition, in most instances; and also how to prevent such conditions. Such studies have also given us much knowledge of the suitability of most foods in controlling or preventing the general types of digestive disturbance that I have mentioned, and they have taught us an appreciable amount concerning the reduction of the labors of metabolism and excretion through proper choice of foods. We have much yet to learn, but we do not make use of what we have learned. If we can start from the stand-point of learning the general type of the condition that we are dieting, and can then apply the general principles of our knowledge of metabolism and of foods to this, the question of details will afterward become comparatively easy and will be simply dependent on the gradual elaboration of one's skill in details.

The next most impressive dietetic error, it seems to me, is to restrict narrowly or largely exclude most or all the members of a class of foods, because there seems to be an especial difficulty with this class. We commonly encounter the order, for instance, to "stop using starchy foods"; and often, as a result, carbohydrate foods are more or less completely excluded from the diet. Unquestionably we have been clearly taught that a considerable amount of protein is essential, and in recent years we have equally well learned that an even larger amount of carbohydrate is almost as necessary for the proper performance of the chemistry of the body processes and especially in avoiding acid intoxication. A reasonable amount of fat is also at least extremely desirable, because of its great food value. These facts sufficiently indicate that our efforts should not be directed toward the exclusion of the whole of a peccant class of foods, in case some of the class disagree. We should, on the contrary, develop sufficient knowledge of food composition and food preparation to be able to choose from the troublesome class varieties that will themselves agree. This we can usually do.

It should be our chief effort to keep the amount of each class approximately near the normal, except when temporary complete rest from some one class appears to be needed, as occasionally happens. If wide variations from the normal are very harmful, it is probably true that even moderate variations from the normal are at least disadvantageous, especially if persisted in.

Such are some of the main principles that we can derive from dietary studies, but there are many other points that could be discussed. For instance, simple intake and outgo experiments have shown that it is exceedingly difficult to make a normal person gain in protein tissue by feeding, but they have demonstrated how greedily the convalescent retains protein. He is in much the same state as is the growing child in this regard. A proper appreciation of such a point as this makes one realize much more clearly that by taking advantage of this tendency and wisely pushing matters in convalescence we can not infrequently transform a disease from a curse into a blessing by keeping metabolism on the run, so to speak, thus making tissue growth go farther than the previous amount, and changing a person previously ill nourished into one whose nutrition is comparatively good. The same principle holds with the infant. Not only does the infant or child retain large amounts of protein; this very fact, as well as simple reflection, indicates that large amounts are needed at this period of life, and I firmly believe that in recent years the minds of pædiatrists have been so fixed on the digestive tract and on the dangers of high protein feeding that general nutritional demands have been half forgotten and many infants have been injured by giving them too little protein.

There are numerous other ways in which a knowledge of metabolism, even though it cannot be so directly translated into action, is nevertheless indirectly influential in determining a broad and comprehensive action instead of a narrow and mistaken one. One of the simplest instances of this, for example, is diabetes. We are much better off clinically to know that there is no evidence, except in the late and grave stages,

of a toxic tissue destruction in diabetes; that treatment directed to the elimination of a toxæmia would be superfluous, and that the anomaly, whatever its actual nature may be, appears in ordinary instances to produce a tissue loss simply because there is a food loss due to the glycosuria, and the glycosuria largely explains all the other typical symptoms, even the acidosis and the coma that may occur. This makes much more clear the entire dependence of successful treatment on diet.

The severity of the disturbance in various diseases has often been made clearer by balancing figures against each other. One of the most striking instances of this that I have ever seen is a case of simple purpura that I have recently studied, one of the type that affords no clinical evidence of constitutional disturbance and hence is said to have no constitutional symptoms. This patient, when studied metabolically, showed a high grade of tissue loss with each outbreak of purpura, demonstrating clearly that he had severe metabolic disturbance and that some metabolic disorder produced his attacks; for the amount of hemorrhage was not sufficient to have been of itself responsible for the disturbance of metabolism.

The effect of different forms of treatment can frequently be made much more apparent by studies of this sort. For instance, I have recently investigated a case of direct transfusion by Crile's method, in which the clinical results and the effect on the blood indicated solely improvement in the patient's general condition and his blood count. A metabolism study, however, showed very striking tissue destruction, with some features that indicated that it was almost certainly not due merely to a breaking down of the transfused blood, thus showing that the effects of this operation may at times, in diseased persons at least, be much more extensive than merely to provide more blood for the patient, and it would seem that these effects may occasionally be very dangerous, for when a second transfusion was done in the same patient death speedily followed. Similarly, I have acquired a much more serious respect for the effects of the X-ray from having observed the remarkable influence that it can exert on metabolism, and having seen

how easy it may be for the X-ray to cause tremendously good or dangerously bad results in ways that are not readily made apparent through ordinary clinical observation or through other methods of study.

The results of simple intake and outgo estimations often, too, make more apparent the nature of conditions, and especially whether there are or are not evidences of toxic tissue destruction, and, therefore, whether we can wisely use eliminative measures, or whether these would probably be positively harmful because not indicated. These are instances of the numerous ways in which metabolism studies of the simplest form—namely, balancing intake against outgo—have influenced our clinical conceptions of disease and of the manner in which various kinds of disease should be managed. There is, however, a vastly broader aspect of metabolism investigations.

Beyond all other things it has always been apparent, and in recent years more and more evident, that in order to gain an intimate acquaintance with metabolic processes in normal or diseased persons we must not limit our studies to a comparison of the intake and outgo, and to a determination of the grosser changes in the excretions, the body fluids and the tissues, but must acquire a closer knowledge of the intermediate changes that occur in the course of digestion and in the synthesis and breaking down of tissue, and must learn the kinds of things that favor or interfere with these processes. Many tentative efforts were made to do this, but the tangible knowledge that they provided was slight, because the work was done somewhat blindly, until within the past few years, when two remarkable changes have occurred in our point of view and have opened the threshold to a new era in studies of metabolism.

TISSUE FERMENTS.

One of these is the conception we now have of the activity of ferments in tissue processes, a conception originally due to Salkowski's initiative; the other, the conception that we now have regarding the constitution of the protein complex, the meaning of the changes in protein that occur in digestion and

metabolism, and their bearing on the breakdown and synthesis of tissues—a conception that was in the beginning due largely to the work of Kossel and his school, and in more recent years has been elaborated to a marvellous degree by the work of Emil Fischer and numerous others that have worked with him.

It is a striking fact that in the last-issued edition of Neumeister's "Physiologische Chemie" its then prominent author should have felt justified in stating that the observations of Salkowski and others concerning the presence of ferments in the tissues meant merely that these ferments were absorbed from the digestive tract in zymogen form, not that their production had any relation to the essential activities of the tissue cells, and that this statement should have been followed very soon after by the address of Hofmeister in which he predicted that it would be shown that most tissue processes, synthetic or catabolic, are largely dependent on the activities of ferments produced in the tissues. A few years ago we looked on ferment processes as confined to the digestive tract. Now the very name "digestive tract" so far as it applies distinctively to the kind of processes that go on in the stomach and intestines, has become almost a misnomer, for it has been made apparent that the same general kind of processes go on in the tissues everywhere, products similar to those produced in the alimentary tract being formed by ferments similar to the so-called digestive ferments. The distinction between digestive and tissue processes, even synthetic tissue processes, has grown still more indefinite since we have learned the influence of ferments on synthetic processes, and especially since it has been actually demonstrated through the work of Croft Hill, Kastle and Loewenhardt, and Alonzo Taylor, that individual carbohydrate, fat, and protein ferments do really have the function of building up, as well as of breaking down—that the same ferment does either of these two apparently opposite things, the result being dependent on the conditions in which it acts, and not on the nature of the ferment itself.

The profound emphasis thus laid on the importance of the study of the conditions in which ferments act, directs atten-

tion particularly to the exaggerated optimism that has somewhat generally, among clinicians, been centred on securing and using therapeutically ferments that are active in tissue processes. Even scientific workers have held forth alluring prospects in this connection. As a matter of fact, we cannot manufacture substances that are so dependent on life processes for their existence as are tissue ferments—that often, indeed, are probably dependent on the unchanged structure of living protoplasm. We cannot be sure that we shall ever be able to separate most of them in satisfactory form; and when we get them, as we do now, they are usually damaged and made more or less ineffective, often destroyed, by the processes through which they are put; and even if we secure them in satisfactory condition we have not yet obtained the slightest reliable evidence that we can, to any noteworthy degree, influence tissue processes by their therapeutic use. We even have no satisfactory evidence that their use influences digestive processes in the alimentary tract to any noteworthy degree. We have, therefore, it appears to me, excellent reasons for being very guarded about basing any serious hopes on the use of ferments themselves, in attempting to influence the processes in which they are normally active.

On the other hand, what a wealth of reasonable suggestions for interesting future work is given by the fact that it is not the ferment itself, but the medium in which it acts, that determines so profoundly important a result as to whether the effect is to be construction or destruction; and what alluring possibilities in the distant future are offered by this as to the possible control of nutritive processes and of disease. It is highly probable that it is merely a change in medium that causes previously existing ferments, which have been inactive, to become suddenly active after a pneumonic crisis, and to digest the exudate with astonishing rapidity. The same thing is probably true regarding the involution of the uterus that begins with the beginning of the puerperal state. Indeed, it appears to me not improbable (though entirely unproved) that in this instance the change occurs directly from constructive action to destructive, for the growth of the uterus in pregnancy

is a growth, not so much, if at all, in the number of the cells, but merely in the amount of tissue in the cells. It is quite possible that in pregnancy there is a ferment-constructive process, and that in the puerperium destructive work is done by the same ferment or ferments.

Such things are at the present time matters largely of speculation. I speak of them only in that sense and mention them merely as illustrations of what such studies may ultimately lead us to in regard to our powers of controlling normal nutritive processes and disease. We already know great numbers of things that influence ferment processes, and it is not improbable that we even now have in our armamentarium things that have much greater powers in this regard than we at all appreciate, and that we may gradually learn to make proper use of these powers, if we proceed from the correct point of view, and not merely from blind empiricism.

One way in which it appears to me to be probable, though as yet undemonstrated, that we actually do control, to some extent, the medium in which the ferment action takes place, is in the management of some of those cases in which acid intoxication occurs. The acidosis of diabetes appears to be largely dependent on the diet and on the inability of the organism to make use of carbohydrates, and it is possible that it is entirely dependent on these things, but there are numerous instances in which diet seems to be a factor of very little, if any, consequence in producing the acid intoxication that occurs as a part of the disorder—cases such as phosphorus poisoning and acute yellow atrophy, uræmia, the recurrent vomiting of childhood, post-anæsthesia acidosis, grave anæmias, and probably the pernicious vomiting of pregnancy. A number of these disorders seem, from accumulating knowledge, to be associated with tissue lesions and with alterations in metabolism that indicate that there is an abnormal activity of the proteolytic tissue ferments, particularly in the liver, and that this autolysis probably produces the acid intoxication secondarily. The acid intoxication in all probability then, in its turn, increases the autolysis, for Hedin and Rowland, and others, have shown that a

slight acidity favors autolysis. Thus it is probable that a vicious circle is formed, and the effects increase from their own momentum. This conception is practically an application of the knowledge regarding autocatalysis to pathology. Clinically, in some of these cases, direct treatment of the acid intoxication with alkalies does good, but their action is most uncertain and unreliable. In bringing forward the evidence that acid intoxication is seen in the recurrent vomiting of children, I reported cases in which alkalies unquestionably did great good, and I have observed some such cases since; but the result is highly uncertain and cannot be anticipated. It appears to me somewhat probable that what we actually do in some of these cases by means of alkalies is to control whatever evil effects there may be as a direct result of the acid intoxication and, what is much more important than this, to provide a less favorable medium for the autolytic ferments to act in. If this is true, it is probable that the results are uncertain largely because the destructive changes that have already resulted from autolysis are so variable in their degree. If they have not been severe, the symptoms, no matter how severe they may be, will be controlled by stopping the progress of the ferment action; but if severe lesions have already occurred, no matter how mild the symptoms may be, control of the primary condition will not control its already grave destructive effects.

I have suggested another direction, also, in which it is possible that our study of the means of accelerating or retarding ferment action may have interesting clinical bearings. I have expressed the view that the X-ray exerts its action on the deeper-lying tissues, in part, at least, through influencing ferment action. This is by no means definitely proved, but there is some creditable evidence in favor of it. Starting with this conception, I have studied the effects of the X-ray in a condition in which our knowledge indicates that the desirable but hitherto often unattainable therapeutic measure is to accelerate or excite ferment action; namely, in unresolved pneumonia. Unquestionably the X-ray has had a very remarkable effect on metabolism in cases of this kind that Dr. Pemberton and I have

studied, and there has apparently been a very strikingly good effect clinically on the consolidation in the cases that I have so far observed. My conclusions may be wrong in these instances, but I think that these are examples of the interest and the possible profit pertaining to systematic attempts to work out practical methods of influencing tissue ferments.

Similar studies will not improbably help us to understand the manner of action of things that we have already used without comprehending the way in which they accomplish their unquestionable effects. Unpublished observations that Dr. Caspar Miller and I have made indicate that the remarkable effects of mercury in acute poisoning, and probably in syphilis, are, partly at any rate, due to its causing increased autolysis, a suggestion that Dr. Flexner made publicly while we were working on this matter. Also some studies that I have not as yet completed, suggest that one way in which sunlight produces its pronounced effects on nutrition is through its influence on the same kinds of processes.

STUDY OF PROTEIN-COMPLEX.

Closely interlaced with the investigation of the tissue ferments is the study of the protein-complex and the products that it yields on digestion. Biological observations have made it apparent that there are differences in the proteins of various species that simple analytic chemical methods do not show. The studies of recent years have probably demonstrated what the most important chemical differences are. Proteins of different species may or may not differ in the amounts of nitrogen, hydrogen, oxygen, sulphur, phosphorus, and other elements that they contain, but this is not the essential question. A Norman and a Gothic cathedral may contain the same amount or different amounts of stone, mortar, and glass. The essential characteristics of the architecture of such structures are not determined by the total bulk of the primary substances of which they are made, but by the manner in which the stone and mortar and glass are first put together to make columns, windows, and other parts of different forms, and by the manner

in which these are then employed in completing the whole. So in various proteins are the chemical elements first put together to form simple structures, the various amino acids, and these are then joined together in various amounts and to some extent in various kinds to form the different varieties of protein. Digestion consists in the fragmentation of the complex structures into the simpler structures. These latter are then put together in different amounts, and to some extent, different kinds, to reconstruct the variety of protein desired.

This entirely alters our conception of digestion. Previously we thought of it practically as merely the hydrolysis of protein into forms that are dialyzable, and the purpose appeared to be simply to get protein into such a state that it could pass animal membranes and get into the circulation. The serious subject of discussion was chiefly where and how the building-back into native protein occurs, for albumoses and peptones could apparently not enter the circulation, since they have toxic effects. Our present conception of the chief purpose of digestion is that it breaks down foreign protein into the parts that make up the whole, in order that these parts may then be used in suitable amounts in reconstructing protein of the structure proper in the individual that is to be nourished.

It is highly probable that in abnormalities of this process of fragmentation and reconstruction we shall find the causes of some nutritional disturbances. We are all familiar with instances of digestive disorder associated with more or less profound nutritional disturbance, and we know that the disorder of nutrition may be vastly more severe than the apparent disorder of digestion. I have recently described cases of infantile atrophy and other obscure forms of emaciation in which the proteolytic ferment powers of the intestine were greatly reduced—whether as the result of actual absence of proteolytic ferment, or because other conditions of the contents of the intestinal wall in these cases were unsuitable for ferment action, I do not know. In other forms of extreme emaciation of known causation, the ferment activities were normal. I have since investigated further cases that have given the same results.

These observations lend some support to the hypothesis that I have suggested, that disorder in the fragmentation of the protein food or in the reconstruction into circulatory or tissue protein, or in both these processes, may prove to be the chief explanation of the nature of such conditions.

In matters such as these we are wandering in regions that are as yet too little explored for us to be able to come to very definite conclusions as to the meaning of results that have already been obtained, and we cannot yet ask that the practical application of this knowledge in diagnosis and treatment should be at all clear. We have a glimpse, however, of the possibilities of productive work that will bear directly on our conception of normal and disease processes, and that will probably in time greatly increase our powers of recognizing the nature of disorders and will ultimately lead to enlarging our powers of controlling them.

Our knowledge of the activities of ferments in the tissues and our present conceptions of the protein-complex and its changes in digestion have already entirely altered our conceptions of the nature of many normal tissue processes and of numerous diseases. The manner in which the most striking lesions are produced in phosphorus poisoning and acute yellow atrophy has become clear; indeed, acute yellow atrophy has been practically transformed from an obscure disease into no distinct and separate disease at all, but a severe and striking stage of a process that occurs in varying degree in various circumstances, and that appears clinically to be a distinct disease only when the autolytic changes become so severe and progressive as to be the reigning process. We have reason to hope that this conception of acute yellow atrophy will guide us to work out clinically much more clearly the early stages of the condition and its exciting causes, and ultimately may help us to intervene effectually at a period when dangerous lesions have not yet occurred. I think that we may have similar hopes in such conditions as recurrent vomiting, probably in the pernicious vomiting of pregnancy, in intoxications following anæsthesia and in some other disorders, distant though the consum-

mation of such hopes may be. Indeed, the studies made by Howland and Richards, which are highly suggestive in a number of ways, have already furnished some important practical suggestions as to what should be done and what should not be done in the avoidance of the intoxication following anæsthesia and to some extent in the treatment of this condition when it has actually appeared.

METABOLISM OF INORGANIC SUBSTANCES.

Another broad field that is only beginning to be cultivated in an understanding way is the metabolism of the inorganic substances found in the body. We know as yet very little in regard to this subject that can be used in any clinical way, but the remarkable researches of Jacques Loeb especially have led to information regarding its importance in elementary physiologic processes, particularly in the lower forms of life. His work makes it evident that it must come to have highly important clinical relations, and the studies of Alonzo Taylor of the effects in the human being of a salt-free diet are sufficient evidence of the profound effects that alterations in salt metabolism may produce and of the clinical interest that attaches to investigations of the physiology and pathology of this question. Various other studies are likewise extremely suggestive in this relation and the marvellous effects of the antagonism between calcium and magnesium that Meltzer has demonstrated make the developments in this field of still more intense and immediate importance.

CONCLUSIONS.

The actual clinical bearing of all these things that I have mentioned in this latter portion of my remarks still lies chiefly in the greater breadth that they have given us in our conceptions of the nature of normal and diseased processes. Their direct bearing on such practical things as diagnosis and treatment is slight. But we cannot ask that clear and especially that comprehensive clinical relations should yet be evident. They touch so closely on the things fundamental in understand-

ing life itself that to ask that their bearings shall all be made clear in the span of a man's life is equal to asking that in the same period of time all the world shall reach that "far off divine event to which the whole creation moves." But, as I have indicated, we shall be able gradually to accumulate a few facts here and there that will be directly available in practice if the proper principles are followed, even though obscurity still surrounds most of the details, and at any rate broad conceptions that lead to a more correct general line of action are, all in all, more valuable to the clinician than are a few detailed additions to our direct diagnostic and therapeutic methods, even though these additions accomplish their special purposes very effectually. In witness of this I would mention the great value, on the one hand, of a general comprehension of the influence that can be exerted in the prevention and cure of many infectious diseases, for instance tuberculosis, through general measures directed toward increasing the resistance of bacterial growth and toxin action; and, on the other hand, the relatively slight importance in the general course of practice of those details that have been developed regarding the scientific special treatment of most such special infections.

I have pictured a very incomplete and hasty view of the relations between metabolism and clinical medicine. If I am criticized, as may readily be done, for having made my attitude toward my subject one of championship rather than of exposition, I would say that I have done this deliberately, for I feel that, in past years especially, and to a large extent even now, the teaching of subjects that bear on metabolism has, much more than is the case with most other subjects in medicine, been such as to give some knowledge of details and methods, but not such as to give a comprehension of the philosophy of metabolism studies in their bearing on clinical conditions.

THE CHEMICAL CONTROL OF THE BODY *

ERNEST H. STARLING, M.D., F.R.S., F.R.C.P. (Lond.),
Todrell Professor of Physiology in the University of London,
London, England.

THE desire of man for life, a necessary condition of existence in a healthy animal, has led him to search out by experiment the secret workings of his own body, with a view to acquiring by more perfect knowledge a measure of control over his own functions, comparable to that which he has already obtained over the forces of inanimate nature. In this way has been founded the science of medicine, the pursuit of which is the main object of the members of this society. Among the methods devised to this end, viz., the control of the functions of the body, must be classed the whole treatment of man from his youth upward; and a large part of the efforts of the medical man must coincide with those of the educationalist and the sanitarian in the endeavor to assure health by measures which affect, in the first place, the environment of man, his patient.

In the eyes of the general public, however, the office of the medical practitioner is often limited to the, for the present, less important rôle of administrator of medicines or drugs. Although this method has been the main weapon of the "medicine-man" in his fight against disease from the earliest ages, its scope is still but limited, and only within the most recent times has any attempt been made to place it on the basis of actual knowledge. The empirical character of the greater part of the treatment by drugs has proved a potent weapon in the hands of the satirist of the medical profession, and exception has often been taken to the employment of chemical remedial measures as being utterly opposed to the laws of Nature and

---

* Lecture delivered January 11, 1908.

the methods employed by her in the regulation of the body processes and the reaction of the organism against disease.

I wish to call your attention to a whole array of facts which demonstrate the unjustifiability of this attitude. As a result of recent investigations, we may assert that in the employment of drugs we are but imitating, although perhaps in a very imperfect manner, the method employed by Nature herself, and, indeed, that a large share in the wonderful co-ordination of the activities of different parts of the body, which determine their mutual co-operation for the common weal of the organism, is played by the production and circulation of chemical substances which are strictly analogous to the drugs employed during countless ages by mankind in the treatment of his diseases.

The idea that chemical factors must play an important part in the correlation of function between different parts of the body is not new, but I do not think its full significance was realized before the discovery of a very perfect and simple example of chemical co-ordination, viz., that by means of which the activity of the pancreas is determined according to the nature or extent of processes occurring in the alimentary canal. I may, therefore, perhaps, be allowed to give you a brief account of this mechanism before treating of the numerous other instances of chemical correlation, many of which have been long known, although even now we cannot pretend to a full comprehension of their significance in the body.

Among the many important discoveries of Pawlow and his school on the physiology of digestion, one of the most striking was the fact that the introduction of dilute acid into the duodenum and upper part of the small intestine provoked secretion of pancreatic juice, just as the introduction of acid into the mouth excites secretion of saliva. Thus, as fast as the acid chyme passes into the duodenum, its presence in the latter organ provokes a flow of alkaline pancreatic juice which will continue until the chyme is neutralized.

We know from the researches of von Mering, Cannon, and others that so long as the contents of the duodenum are acid the pylorus remains closed, so that we have here a chain of processes

determining a gradual emptying of the stomach into the duodenum and the addition to the chyme of just sufficient pancreatic juice to neutralize it and stop the action of the gastric juice and to bring about pancreatic digestion in full activity.

The "acid reflex" from duodenum to pancreas was ascribed at first by Pawlow to the intervention of a reflex arc of which the vagus was the efferent nerve. His pupil, Popielski, almost simultaneously with Wertheimer of Lille, showed that the "reflex" can be brought about after severance of all connection between the alimentary canal and the nervous system. These observers regarded the phenomenon, therefore, as brought about through a local reflex arc involving peripheral nerve-centres. Bayliss and I at first accepted this interpretation. We were interested in the phenomenon as possibly showing an influence of the local nerve-centres, whose action on intestinal movements we had just studied, on the chemical processes of the gut and its appendages; and we, therefore, sought to determine the conditions of the reflex more closely.

We found, however, very soon that the experiment could be so devised as to exclude any possible intervention on the part of either the central or the peripheral nervous system, and yet obtain secretion from the introduction of acid into the gut. Thus, if a loop of the jejunum be tied at two ends, and all its nervous connections severed, so that it remains attached to the rest of the body simply by the blood-vessels, introduction of acid into this loop evokes a flow of pancreatic juice as marked as that obtained from the introduction of acid into a normal loop. Since the message from the gut to the pancreas, arousing its activity, cannot reach it by way of the nervous system, the only possible channel left is the blood stream; and the messenger must, therefore, be some chemical substance discharged into the blood stream, and not a molecular change propagated along nerve-fibres. That the messenger cannot be the acid itself was easily shown by injecting acid into the portal vein, when no effect was produced.

We see, then, that acid introduced directly into the blood has no effect, while if it be injected into a cavity separated

from the blood by only the epithelial cells of the intestine it has an effect. The chemical messenger, therefore, must be something produced in the epithelial cells under the action of the acid and discharged by them into the blood stream. This conclusion was speedily realized. When we scraped off some of the epithelium, rubbed it up with acid, and injected the hastily filtered mixture into the blood stream of the animal, a flow of pancreatic juice was obtained considerably greater than any we had hitherto obtained as the result of injecting hydrochloric acid into the lumen of the intestine.

To this chemical messenger we gave the name of "secretin." In order to obtain it free from admixture with the protein constituents of the cells, the ground-up intestinal epithelium was boiled with 0.4 per cent. hydrochloric acid and while boiling was neutralized. In this way all the coagulable protein was thrown down. The filtrate was found to exert a strong exciting effect on the secretory activities of the pancreas.

This mode of preparation shows that secretin is neither a ferment nor a protein. Other experiments have shown that, while fairly stable in acid solution, it is very rapidly destroyed in alkaline solution. It is soluble in fairly strong alcohol, or alcohol and ether, but is insoluble in absolute alcohol. It is fairly diffusible through parchment paper and is not precipitated by the ordinary alkaloid precipitants. The ease with which it undergoes oxidation has hitherto foiled all attempts to isolate it in a pure form; but the properties mentioned suggest that it is a body of comparatively low molecular weight, and that it ought to be possible to obtain it in crystalloid form. In much of its behavior it resembles adrenalin, the isolation of which presented at first many difficulties, but was finally successful in the hands of Takamine. This body, secretin, can be regarded as a type of a whole group of chemical messengers, which, formed in one organ, travel in the blood stream to other organs of the body and effect correlation between the activities of the organs of origin and the organs on which they exert their

specific effect. For these chemical messengers we have suggested the name of "hormone," from ὁρμάω, I arouse or excite.

It may be remembered that Ehrlich divided the chemical agents which act on the organism into two classes, which we may shortly describe as the toxins and the drugs. As a type of the first class, we may instance a poisonous constituent of jequirity, which has been called abrin; and of castor-oil seeds, ricin; as well as the toxic products of pathogenic micro-organisms, such as the well-known toxins of diphtheria or tetanus. All these bodies introduced in minimal doses into the organism evoke characteristic effects either local or general. The specific character of their physiologic action suggests that these toxins have special affinities for one or other tissue of the body, affinities conditioned by their chemical character as well as by that of the affected organs.

In this respect they are entirely analogous to the drugs which form the main part of our pharmacopœias, and of which we may take strychnine, morphine, or arsenic as types. There is, however, one marked distinction between the two groups. When repeated small injections are made of a body belonging to the group of toxins, the physiologic effect produced becomes progressively less, and it has been established that the immunity to their action which is thus brought about is due partly, at any rate, to the formation of substances in the organism which are the physiologic antagonists of the toxins and have the power of combining with and neutralizing these substances.

Thus, if the blood-serum of an animal rendered immune by repeated doses of diphtheria toxin is mixed with some of the diphtheria toxin itself, the resultant mixture, which may contain many hundred times the lethal dose of toxin, may be injected into an untreated normal animal without producing any effect. Although in the case of certain of the drugs, such as morphine, a limited degree of tolerance may be established, there is no evidence of the production at any time of antitoxic substances in the treated animal.

Now, it is evident that if a substance is to act repeatedly as a chemical messenger through the medium of the blood be-

tween one organ and another, its function would be abolished if the discharge of the chemical message into the blood stream gave rise to the production of an antibody. These chemical substances, or hormones, must, therefore, as a necessary condition of their function, belong to the class of drug substances, generally crystalline, or at any rate not belonging to the colloid class, of definite chemical composition, and in most cases of comparatively low molecular weight. Their action on the chemical basis of the protoplasm must be determined by their molecular structure, and in all probability must be ranked with the purely chemical processes, rather than with those mixed chemical and physical processes which determine the formation of absorption compounds and distinguish the interaction of one colloid with another, as well as of toxins with the animal cell or with their corresponding antitoxins.

It is only necessary to remind one of a number of well-established correlations of function effected by the intermediation of these hormones in order to carry conviction of the very large part that they must play in the normal processes of the body. In the alimentary canal itself, the chemical correlation between intestine and pancreas does not stand alone. Thus, Pawlow showed that the secretion of gastric juice occurs in two phases, the first phase being excited through the vagus nerve by appetite, or by impulses from the mouth, while the second phase was determined by the presence of certain substances in the stomach. Edkins has shown that the secondary secretion of gastric juice is determined by the production of a hormone in the pyloric part of the mucous membrane under the influence of the first products of digestion, and that this hormone is absorbed by the blood and carried by it to the gastric glands of the fundus, which are thereby excited to renewed activity.

The secretion of the intestinal glands is partly excited through the local nervous system by the mechanical stimulation of the mucous membrane. It is probable, however, that the pancreatic secretin formed in the duodenum, and perhaps other hormones produced in the intestine, have a direct action through the blood on the secretory processes of the small bowel. The

simultaneous presence of bile and pancreatic juice in the duodenum, which is necessary for the full unfolding of the digestive activity of these juices, is secured by the fact that the secretin formed in the intestinal mucous membrane under the influence of the acid chyme, has a specific excitatory effect not only on the cells of the pancreas, but also on those of the liver. The postprandial rise of biliary secretion is synchronous with the postprandial rise of the pancreatic secretion, and in both cases the secretion is determined by the secretin circulating in the blood as the result of the action of acid on the cells of the duodenal mucous membrane.

It is possible that chemical factors play an important part not only in arousing the secretion of the digestive juices, but also in determining the absorptive activity of the intestinal epithelium. I do not see how otherwise we are to explain the remarkable effects on the absorption of the foodstuffs which ensue on the total extirpation of the pancreas. Whereas ligature of the ducts of this organ leaves the absorption of foodstuffs, other than fats, practically unaffected, its total extirpation diminishes by one-half the absorption both of carbohydrates and proteins and almost entirely annuls the absorption of fat.

When we pass to the other functions of the body, we find many other instances of correlation by undoubted chemical means, as well as instances in which, with our present knowledge, we can find no other explanation of observed phenomena than the assumption of such chemical means. Perhaps the best marked case is that presented by the regulation of the respiratory movement in accordance with the needs of the organism, especially of the muscles for oxygen.

The increased depth and frequency of respiration contingent on muscular exertion are familiar to every one, and we know that the physiologic object of such changes is to secure the increased ventilation rendered necessary by the enormous rise of gaseous metabolism which accompanies muscular exercise. Even moderate work may raise the gaseous exchanges to between four and eight times their amount during rest. This increase in the respiratory movements is entirely involuntary,

and may, in its earlier stages, when affecting chiefly depth of respiration, be unnoticed by the subject of them.

How is the respiratory centre aroused to an increased activity which is strictly proportional to the increased metabolism of the distant muscles? A nervous path is at once excluded by the fact that hyperpnœa or even dyspnœa may be excited in an animal, after division of the spinal cord, by tetanization of the muscles of the hind limbs. Zuntz and Geppert, therefore, came to the conclusion that the exciting agent in this increased activity was some acid substance or substances produced by the contracting muscles and transmitted from them through the blood stream to the respiratory centre.

The subject has been investigated lately by Haldane and Priestly. In a series of masterly experiments these observers show that the chemical messenger in this case is none other than carbon dioxide. The contracting muscle, when properly supplied with oxygen, takes up this gas and gives out carbon dioxide in direct proportion to the energy of its contractions. The carbon dioxide, diffusing rapidly into the blood stream, raises its percentage and, what is still more important, its tension in this fluid. The respiratory centre differs from the other parts of the central nervous system in having developed a specific sensibility to carbon dioxide. Its normal activity is determined by the normal tension of this gas in the blood and lymph bathing the centre. Diminution of the tension of this gas depresses the activity of the centre, causing slackening of respiration, or even the total cessation of respiratory movements, known as apnœa.

This work by Haldane may be regarded as finally deciding a question which has been the subject of debate for nearly half a century. The dyspnœa, caused by the circulation of venous blood through the brain or by the deprival of the respiratory centre of the means of maintaining its normal gaseous interchanges, has been variously attributed either to oxygen starvation or to carbon dioxide intoxication of the centre. Haldane shows that the centre is very little sensitive to changes in the oxygen tension of the blood. The oxygen tension in the

pulmonary alveoli may be altered from 20 per cent. to 8 per cent. without any increase in the depth or frequency of the respiratory movements. In these circumstances the heart or circulatory system may feel the deprivation of oxygen before the respiratory centre has responded to it. On the other hand, a rise of only ½ per cent. in the tension of carbon dioxide in the alveolar air, and, therefore, in the blood circulating round the respiratory centre, will increase the volume of air respired 100 per cent.

This simplest of all examples of a co-ordination of two widely separate organs by chemical means may, perhaps, give us a clue to the mode in which the more complex of such correlations have been evolved. The chemical messenger is here a product of activity which is common to all protoplasm and must be excreted by the cell as a condition of its further activity. The adaptation in this case, therefore, is not the formation of a special substance which shall exert a specific influence on some distant organ, but the development in this distant organ of a specific sensibility to the common product of excretion of the first organ. We may, perhaps, assume that the more specialized messengers, which we shall have to consider in detail later, were at first accidental by-products of the selfish activity of the organ producing them, the first step in the development of a correlation being the acquisition of a sensibility to the substance in question by some distant organ.

The only other example of such a reaction, in which we know both the source and nature of the chemical messenger and the exact nature of the effects which it produces, is the suprarenal gland. Since the time of Addison we have known that atrophy of these glands in man leads to a disease characterized by the three cardinal symptoms of bronzing, vomiting, and extreme muscular weakness. Most of the attempts to reproduce this disease in animals have failed, owing to the fact that death follows the excision of both glands within 24 hours; the extreme muscular weakness is certainly produced, and this is attended by a profound fall in the general blood-pressure.

In 1894, Oliver and Schäfer showed that from the medulla

of the suprarenals a substance could be extracted which, on injection into the circulation, caused a marked rise of blood-pressure and increased strength of the heart-beat. Since the publication of these observations, our knowledge concerning the nature and actions of this substance has progressed rapidly. The researches of Jowett, of von Fürth, and others have shown that the active substance is a definite chemical compound derived from pyrocatechin and having the formula: $(HO)_2.C_6H_3.$-$CHOH.CH_2.NH.CH_3$.

Dakin has synthesized a whole array of substances which are closely allied to this body in their chemical structure as well as in their physiologic influence on the animal organism.

In order to comprehend the point of attack of adrenalin, the specific secretion of the medullary part of the suprarenal glands, we shall do well to go back to the mode of development of these organs. It was shown by Balfour that the suprarenals have in the fœtus a twofold origin, the cortex being derived from the mesoblastic tissue, known as the intermediate cell-mass, while the medulla is formed by a direct outgrowth from the sympathetic system, and consists, at first, of an aggregation of neuroblasts. In some animals, *e.g.*, teleostean fishes, the two parts of the gland thus formed remain separate throughout life; but in the higher vertebrates the sympathetic outgrowth becomes surrounded by the cortex and the cells rapidly lose all traces of resemblance to a nerve-cell. But the medulla is genetically part of the sympathetic system, and its specific secretion, adrenalin, has an action which is apparently confined to the sympathetic system. In whatever part of the body we test the effects of adrenalin, we find that they are identical with the results of stimulating the sympathetic nerve fibres which run to that part. Thus, in all the blood-vessels of the body, adrenalin causes constriction; the contraction of the heart muscle is augmented, the pupil is dilated, while the intestinal muscle, with the single exception of the small ring of muscle forming the ileocolic sphincter, is relaxed. The action of the sympathetic on the bladder differs, as shown by Elliott, markedly in various ani-

mals; but, whatever its effect, a similar one will be produced in the same animal by the injection of adrenalin.

I have already mentioned that excision of the suprarenal bodies causes a profound fall of blood-pressure, which continues until the death of the animal; and it has been stated that, when this fall is well established, it is impossible to raise the blood-pressure by stimulation of the splanchnic nerve, or, indeed, to produce any effect at all on stimulation of the sympathetic nerve. Thus not only does adrenalin excite the whole sympathetic system in its ultimate terminations, but its presence in the body as a specific secretion of the suprarenal bodies seems to be a necessary condition for the normal functioning, by ordinary reflex means, of the whole sympathetic system. We are dealing here with a problem which, betraying, as it does, an intimate relationship between nerve excitation and excitation by chemical means, promises by its solution to throw a most interesting light on the nature of the nerve process and of excitatory processes in general.

Our knowledge of certain other members of this group of chemical reactions is so shadowy that a mere mention of them will suffice. As an antithesis to the vasoconstrictor action of adrenalin, we find that every organ, when active, is supplied with more blood in consequence of a vasodilatation of the vessels which supply it. In certain instances, Bayliss and I have found that boiled extracts of organs, when injected into the circulation, may evoke vasodilatation of the same organs of the animal under investigation; and we have suggested that the normal vasodilatation accompanying activity is brought about in consequence of the specific sensibility of the arterial walls to the metabolites of the organ which they supply. Too much stress, however, cannot be laid on these experiments, since a more extended series by Swale Vincent has failed to give a general confirmation of our results.

The severe diabetes, which, as shown, by Minkowski, can be produced in nearly all animals by total excision of the pancreas, has been held to denote the normal production in this organ of some substance which is indispensable for the utiliza-

tion of carbohydrates in the body. All efforts to obtain a more exact idea of the nature of this pancreatic substance or influence have so far proved in vain. Ordinary sugar, when placed in contact with extracts of muscular tissues, undergoes oxidation; and Cohnheim states that this process is much accelerated if an extract of pancreas be added to the extract of muscle. A repetition of Cohnheim's experiments by other observers has shown that the effect is so small as to be almost accidental; and we must, therefore, regard the nature of the pancreatic influence on carbohydrate metabolism and the causation of pancreatic diabetes as problems still to be solved.

In the case of the pituitary gland we have an organ of, as yet, unknown function, but which we must regard as concerned in determining the activity of widely differing parts of the body, probably by the production of chemical substances or hormones. Pathologically, all we know is that disease of this organ is apt to be associated with overgrowth of the osseous system. As a result of physiologic experiment, we know that from the nervous part of this organ we can extract, as Schäfer has shown, a substance which, like secretin, is unaltered by boiling, and which has a specific action on the secretory activity of the kidney, producing diuresis, which cannot be ascribed simply to the concomitant changes in the circulatory system. This extract, moreover, has a marked influence on the uterus. What part is played by this pituitary influence on these distant organs in the normal working-life of the body we do not know as yet.

So far the chemical adaptations which I have described have resulted almost exclusively in increasing the activity of the responding organ. We cannot, however, draw a sharp line between reactions involving increased activity or dissimilation and those which involve increased assimilation or growth, since under physiologic circumstances the latter is always an immediate sequence or accompaniment of the former.

In a certain number of chemical correlations the primary effect of the hormone is increased growth or assimilation. In these cases, since the assimilative stimulus builds up the re-

sponding organ, its final effect is to increase the activity or functional capacity of this organ. Just as dissimilation brings about later increased assimilation, so increased assimilation brings about later increase of dissimilatory capacity.

The most familiar example of a chemical correlation, evoking the building up of tissues, is that presented by the thyroid gland, though the effects of the chemical substance formed by the thyroid are so widespread, and differ to such an extent according to the age of the animal employed, that a physiologic analysis of its results is still difficult to give. In the growing animal the chemical substance secreted by the thyroid evidently influences the growth of tissues, among others, of the bones; and it is a familiar fact that injection or administration of thyroid to cretins will result in a restoration of the child toward normal, in increased growth of bones, and in development of various functions, including those of the brain and central nervous system. In adults, on the other hand, the most pronounced effect of injection of thyroid is increased activity of the chemical changes of the body, as instanced by the increased nitrogenous metabolism and disappearance of all overgrowth in the subcutaneous connective tissue, such as is present in myxœdema. Although, therefore, the main result of thyroid treatment is to restore normal growth where such has been previously wanting, it is difficult to say whether its primary effect should be regarded as dissimilative or assimilative.

The fact that the thyroid gland can be administered by the mouth shows that the active principle is not destroyed by the gastric juice, and would, therefore, remove this from the proteid class of bodies, and would diminish very largely any probability of the hormone furnished by this gland being of the nature of a toxin. Whether it is represented by the thyroiodin, the organic iodine compound extracted from the gland by Baumann, though probable, is still unproved; and we can only conjecture that in all probability, when isolated, it will be found to belong to the drug class rather than to the toxin class. We are still quite without knowledge as to the conditions which determine the amount of active substance produced in the thy-

roid gland. All we know is that the activity of the thyroid, like that of the suprarenal gland, is essential to the normal development of the functions of the body. Whether we are dealing here with a constant process, or with a chemical reflex similar to those we have studied in the alimentary canal and evoked by some event affecting directly the thyroid gland, we cannot say.

The largest group of correlations between the activity of one organ and the growth of others is formed by those widespread influences exercised by the generative organs on the body as a whole and on parts of the body. The effects of removal of the testes in the male animal on the growth and disposition of the individual have been known for centuries. The experiments of Shattock and Seligman show that the formation of the so-called secondary sexual characters must be due to chemical influences from the gland and not to metabolic changes set up by a nervous reflex arising from the function of sperm ejaculation.

Corresponding results have been obtained in the female by extirpation of the ovaries, double oöphorectomy before puberty not only preventing the onset of puberty and the occurrence of menstruation, but also modifying the future growth of the whole body in the direction of the male character. It has been shown recently by Marshall and Jolly that the changes in the uterus which determine menstruation are probably due, not to ovulation, but to an internal secretion arising from the ovary.

More definite evidence of a direct influence of the ovary on the growth of the uterine mucous membrane has been furnished by the experiments of Fraenkel, as well as those of Marshall and Jolly. At the suggestion of Born, Fraenkel removed the ovaries of rabbits from one to six days after copulation, in order to decide whether the ovary exercised any influence on the growth of the mucous membrane of the uterus and its preparation for the fixation of the ovum. In every case, on subsequently killing the animal, it was found that extirpation of the ovaries had prevented the fixation of the ova. On the other

hand, if the ovaries were removed on or after the fourteenth day of pregnancy, which in the rabbit lasts about thirty days, the animals went on to full time and healthy fœtuses were produced.

The fact that the corpus luteum of pregnancy grows enormously during the first third of pregnancy and then diminishes in size, suggests that this hypertrophy and growth of cells are for the express purpose of influencing the mucous membrane; and Fraenkel states that destruction of the corpora lutea by means of the galvanocautery is as efficacious as is total removal of the ovaries in determining the end of pregnancy. The cells which form the corpora lutea are derived, not from connective-tissue cells, but from the interstitial cells lying immediately outside the Graafian follicles. Their origin is, therefore, identical with that of the interstitial cells of the ovary, viz., from the primitive germinal epithelium.

A still more striking example of growth in response to chemical stimulation from distant organs is afforded by the mammary glands. As is well known, at birth these organs are limited to a few ducts in the immediate neighborhood of the nipple and equal in extent in both sexes. At puberty, in the human female, there is a growth of the breasts, associated with some gland growth, the main increase in size, however, being due to fat. With the occurrence of pregnancy, a true hypertrophy of the gland begins at once and continues steadily up to birth.

In the rabbit, in which we have studied the changes in the gland, it is extremely difficult to find in the virgin even a trace of mammary gland. The nipple is small and undeveloped, and on making serial sections through the nipple the gland is found to be confined to a few ducts not extending more than a few millimetres outside the nipple. No trace of secreting alveoli is to be observed. With the occurrence of pregnancy a rapid growth of the gland appears to begin at once. Five days after impregnation, when it is still impossible to find the impregnated ovum with the naked eye in the enlarged uterus, the mammary glands are marked out as small pink patches about two centimetres in diameter just under each nipple.

9

On microscopic section the gland is found to be made up chiefly of ducts, which, however, are undergoing rapid proliferation. The cells lining the ducts are about three deep and present numerous mitotic figures. At about the fourteenth day the whole of the front of the abdomen is covered with a thin layer of mammary tissue. Branching ducts, with proliferating epithelium, are still the predominant feature on section; but here and there, especially toward the margins of the gland, small secreting alveoli, lined with a single layer of epithelium, are to be seen. After this time the gland grows with ever increasing rapidity, so that at birth, at the thirtieth day after impregnation, the mammary glands form a layer about half a centimetre thick over the whole of the abdomen.

In the virgin rabbit it is impossible to obtain by expression any fluid from the nipples, but from the fifth to about the twenty-fifth day pinching the nipples results in the expression of a clear, colorless fluid. From the twenty-fifth day onward this fluid becomes opalescent, and during the second and third days immediately preceding birth the fluid obtained is typical milk. The appearance of milk is earlier in multiparous rabbits. and in animals where pregnancies succeed each other rapidly it may be possible to express milk throughout the whole of pregnancy.

In the primiparous rabbit termination of pregnancy at any time after the fifteenth day results in the appearance of milk in the mammary glands, a result which has also been observed in the human female under corresponding conditions. That this onset of lactation is not due to any stimuli, chemical or nervous, received by the mammary glands from the involuting uterus or ovaries is shown by the fact that it may be brought on by performing total extirpation of ovaries and pregnant uterus. The essential feature therefore seems to be in this case the removal of the growing fœtuses.

In order to determine the nature of this connection, Miss Lane-Claypon and I carried out a number of experiments in which extracts made from different parts of the immature rabbit fœtuses were injected into virgin rabbits. In a certain

number of cases, where the injections had been sufficiently numerous, we got well-marked hypertrophy of the mammary glands similar to that observed during the earlier stages of pregnancy. From our results we came to the conclusion that the growth of the mammary glands during pregnancy is due to the assimilatory or inhibitory effects of a specific hormone produced in the body of the fœtus and carried thence through the placenta by the fetal and maternal circulations. The removal of the inhibitory stimulus at the end of pregnancy determines the spontaneous breakdown of the built-up tissues, *i.e.*, activity, which in these cells is expressed by the formation of milk.

It is probable that many other instances of chemical correlation will be revealed by future research. Already, however, an enormous material for experimental investigation is afforded by the facts I have already brought to your notice. In only two of the instances of chemical correlation do we know the chemical nature of the hormone. Future research must determine the chemical nature of the hormone in each case, as also the conditions of its formation and the part it plays in the normal chain of events or adaptations which make up the life of the animal organism.

In working out these problems we may look forward to the prospect of increasing power over the functions of the body. The whole of medical science is but a struggle for control of the processes which determine the life of man, and no field seems to me more promising than that over which we have to-day cast a fleeting glance. A knowledge of the whole field would place us in command of the means employed by Nature herself for determining the activities of most of the functions of the body, viz., drugs, or hormones, which effect their purpose and are then destroyed. It was in view of the prospective importance of this field of studies in the future work of the medical man that I have ventured to present the subject at this time.

SURGICAL SHOCK*

GEORGE CRILE, M.D.,
Professor of Clinical Surgery, Western Reserve University,
Cleveland, Ohio.

IN previous communications, especially in the monographs entitled, "An Experimental Research into Surgical Shock," "An Experimental and Clinical Research into Clinical Problems Relating to Surgical Operations," "An Experimental Research into the Surgery of the Respiratory System," and "An Experimental Research upon Blood-pressure in Surgery," I have set forth in detail certain experimental and clinical data relating to surgical shock. With this published work, and certain experimental and clinical researches soon to be published in detail, as a basis, I shall omit theoretic discussion and endeavor to discuss only certain phases of shock in their relation to surgical practice.

We shall assume as our premises that the fall in the arterial blood-pressure is the essential phenomenon; that without a fall in the arterial pressure there is no surgical shock; that the fall in the blood-pressure is due to traumatism of the nerve-tissue and psychic stimuli. We further assume that the ultimate lesions of shock are the same as those of hemorrhage and that for all practical purposes the phenomena of shock are expressions of altered physiologic functions. We shall assume that death from shock, like death from hemorrhage, presupposes the failure of the circulation, producing certain degeneration of the central nervous system; that there is, indeed, but little essential difference, except as to causation, between death from hemorrhage and death from shock. We shall further assume that the fall in the blood-pressure is mainly due to a functional impairment or breakdown of the vasomotor centres; that the

---

* Lecture delivered January 25, 1908.

heart and blood-vessels themselves are only secondarily affected, principally by reason of the anæmia of low blood-pressure; that the cause of the functional impairment or breakdown of the vasomotor centres is due in part to the effect of excessive afferent stimuli and in part to the progressive anæmia of these centres, there occurring a species of vicious circle. We shall further assume that these shock-producing afferent impulses are but little influenced by general anæsthesia, but are totally blocked by cocainization of their conducting paths. We shall dismiss without consideration the symptomatology of shock and shall now briefly consider the differential diagnosis between concealed hemorrhage and shock.

DIFFERENTIAL DIAGNOSIS BETWEEN CONCEALED HEMORRHAGE AND SHOCK.

In the absence of a history of either trauma or bleeding, without evidence of free fluid in cavities, and without a blood examination, is it possible to differentiate with certainty between shock and hemorrhage? We believe it cannot with certainty be done. Are there any characteristic changes in the blood picture which will serve to differentiate?

In shock, the arterial circulation has failed because the blood has accumulated in the veins, especially in the venous trunks; in hemorrhage, the arterial circulation has failed because the blood has left the vascular system. In the one case there is an intravascular hemorrhage, in the other an extravascular hemorrhage. The circulatory phenomena are virtually identical. In a number of clinical observations of the donors during fifty-one transfusions, and in subjects of intentional bleeding, as well as in experimental research in which the blood-pressure of two animals was simultaneously reduced at approximately the same rate by shock and by hemorrhage, and in which continuous observations were made, we were able to draw the following conclusions:

Hæmoglobin.—In shock, there is either slight or no fall, or a rise, in hæmoglobin from the beginning to the end of the experiments; in hemorrhage, there is first a period during which

there is little or no fall in the hæmoglobin; this period may continue until the loss of a fourth, a sixth, or a tenth of a fatal amount of blood. A steady fall in hæmoglobin then begins and continues until death, though the total fall may be perhaps no more than 20 per cent. The fall in hæmoglobin may progressively continue as long even as twelve hours after cessation of hemorrhage.

Red Cell Count.—The red cell count follows rather closely the curve of the hæmoglobin in both hemorrhage and shock.

Leucocytes.—The leucocyte count in shock shows relatively slight changes, although a considerable fall is sometimes noted. In hemorrhage a rising leucocyte count is noted in every instance, beginning promptly, often before the hæmoglobin or red count has altered. In the clinic and in the laboratory there are scarcely any exceptions to the rule of a rising leucocytic count in hemorrhage.

Summary.—Summarizing, then, in the beginning of an acute hemorrhage, the first and immediate change in the blood picture is a rising leucocytosis. A little later the hæmoglobin and the red count begin to fall progressively, continuing up to twelve hours after hemorrhage has stopped. In shock, there is usually no rise in the leucocyte count and little or no change in the hæmoglobin or red count.

Conclusion.—Therefore, repeated and accurate observations upon the blood picture may differentiate between hemorrhage and shock.

ON CERTAIN PREVENTABLE FACTORS.

Physical.—It is axiomatic to state that the better the physical condition the less the shock. In imperative surgery there is no opportunity for improving the physical state. In the surgery of opportunity the physical state may with great advantage be considered. The functional capacity of the important organs should be at their highest degree of efficiency. Hydrotherapy and massage and a sojourn at the seashore may make a safe risk of a doubtful one.

Psychic.—The psychic factor in shock is usually greater

than we are ordinarily disposed to credit. Most patients must necessarily know the risk they are about to assume for the purpose of deciding upon the operation. Once this has been fairly stated and is comprehended by the patient and the decision given, there should be a concerted effort by every one concerned in the operation—the surgeon and his assistants, the anæsthetist, nurses and friends—to give the utmost confidence to the patient as to a favorable outcome. The ideal condition exists when the patient has implicit confidence in his medical adviser, the surgeon, and the hospital, and places himself unreservedly in their hands. Even patients who apparently are stoical and are certain that details will not affect them unpleasantly may be seriously shaken by too much knowledge. Unless specifically desired, the less time for contemplation prior to the operation the better, and particularly the shorter time the patient is in the hospital for more than the necessary preliminary preparations the better. If not fatigued by the journey, entrance to the hospital the day before operation is ample. Over-preparation at the hospital is oftentimes quite as much at fault as under-preparation. From the time that the patient has accepted the operative advice until his discharge from surgical care he should be received by every one coming in contact with him in any capacity with the air of assured confidence which is always contagious. The early morning operation, without time for contemplation, with every preliminary worked out in a smooth running automatic system, without delays in the room when sent for, without a moment of waiting for the anæsthetist to begin, with only a word of assurance from the surgeon, brings the patient to his anæsthetic in the best possible psychic state. Then, too, the persons properly responsible should see to it that there are no messages, no business affairs, no arrangements after the patient's entrance to the hospital.

The antithesis of this is delay, an uncertainty of the hour, the last messages and arrangements, the discussion of the details of the operation, the presentation at the last moment of new phases, problems, and delays and uncertainties on the part of orderlies and assistants in the transportation of the patient to

the operating-room, an inexperienced anæsthetist, haste, bustle, or confusion in the anæsthetizing room, and the clatter of instruments. This is sufficient to give the patient such a psychic shock that, were there no operation performed, the ordeal in itself might require months for recovery. Every one is familiar with the psychic state of the patient who has been wavering in doubt and indecision as to the operation or method, who has been told too much or too little, who is trying to manage the provisional details, and whose psychic state has lost its equilibrium. One can scarcely over-state the importance of the correct surgical attitude of those in charge of the preparation of the patient and the correct attitude of the anæsthetist and nurses, all of which plays a very important rôle in the favorable outcome. The shortcomings of nurses and anæsthetists most frequently take the form of giving so much routine detailed advice as to frighten the patient. Strength lies mainly in sympathy and suggestion. In certain patients, notably the acute Graves's cases, the fate of the operation may be determined by what has occurred up to the time the anæsthetic is begun. Not infrequently a hypodermic of morphine half an hour before the patient is to leave his room may prove of great value.

In certain emotional types of patients it is sometimes useful to keep them occupied by manicuring their nails, by detailed and long-continued toilet, or any attention that consumes time and beguiles away the thoughts of operation. The real test comes in the first stage of anæsthesia. The infinite tact and skill which enables the anæsthetist, by means of suggestion and a faultless technic, sympathy, and assurance, to carry the patient to surgical anæsthesia without a qualm, is indeed a rare gift. Its importance is attested by the esteem placed upon it by most medical men, especially surgeons who are themselves about to undergo a surgical operation. They usually show as much or more concern as to the skill and ability of the anæsthetist as to that of the operator.

Among other predisposing causes of shock is that of exposure of the patient to cold, or what is worse, wet and cold. Warm blankets, ample chest protection, heated tables, prefer-

ably some form of hot-water bed, all play a certain rôle in the conservation of the patient's vital energies. What would be the sensations of an unanæsthetized patient if he were placed upon a cold glass or metal-topped table, covered by a cold, wet sheet, with a third of the body exposed for a period of an hour? Would not any one regard this as an ordeal, and would it not require several days to recover from such gross neglect and exposure? Because a patient is anæsthetized and cannot protest gives us no license to expose him needlessly.

Anæsthetic.—It is abundantly established both experimentally and clinically that the effects of over-anæsthesia, which seriously embarrass the respiration and the circulation, by no means cease when the patient has again returned to a normal surgical anæsthesia. The resistance of the patient to shock is reduced thereby for a period of many hours. Such a miscarriage of anæsthesia, then, distinctly handicaps the operation and must be seriously considered. This is a forcible plea in favor of expert anæsthetists. In the surgical risks in which the margin available for safe surgical trauma of the procedure in question is ample, ether anæsthesia is for the present probably the best; but there are groups of surgical risks in which the margin of safety is so small, or in which it is doubtful if it exists at all, that the greatest amount of *finesse* in anæsthetics becomes necessary; for example, in acute toxic Graves's cases, in the seriously acute infections, in subjects of prolonged infection and abscess, in diabetic gangrene, in intense arterial sclerosis, in the senile heart, in cases of myocarditis, in pulmonary tuberculosis, in advanced nephritis, in the cases of increased intracranial tension, in operations upon the respiratory tract, in operations within the throat and ear, in certain traumatic cases, in obstruction of the bowels, and in many other cases, the anæsthetic problem becomes individualized and will be discussed in some instances in connection with these operations.

The principle underlying this is that full surgical anæsthesia by the routine method is frequently not the best method, and in the cases in which it is administered it must be given with special modifications. The surgeon and anæsthetist should

be able skilfully to employ nitrous oxide and oxygen, local anæsthesia, cocaine, morphine, and modified ether anæsthesia, even psychic anæsthesia, according to the requirements of the case. For example, in acute or chronic pulmonary disease, local anæsthesia, intraneural anæsthesia, or heavy morphine with light ether anæsthesia should, if possible, be used, adapting the method to the operative problem. In strangulated hernia with vomiting, morphine-cocaine anæsthesia should be used; in certain acute traumatic cases, especially of the lower extremities, in deep shock, spinal anæsthesia; in grave acute suppurations in which but little technic is required, nitrous oxide anæsthesia; in exploration for diagnosis in which there are internal lesions, such as gastric carcinoma, morphine-cocaine anæsthesia; in grave cardiac lesions, morphine-cocaine and intermittent ether anæsthesia. Our anæsthetic resources now are so numerous, and modifications and combinations may be so effectively made, that operations that were once unsafe may again be reclaimed.

RELATION OF LOSS OF BLOOD TO SHOCK.

In the normal state in adult life in the horizontal posture, a large amount of blood, often up to 3 per cent., may be lost with little or no change in the blood-pressure, in the pulse-rate, or in the respiration. In infancy and senility, this proportional amount that may be lost with so little apparent effect diminishes in inverse ratio, so that in infancy and old age but little blood may be safely lost. Likewise, as we leave the normal state of health to enter the various grades of many diseases, the margin of safe loss of blood is diminished. In the head-up position hemorrhage is not so well endured. Advantage of this was frequently taken by the phlebotomists of the past, by bleeding their patients standing until they fell. In shock itself the loss of blood is less well endured. The value of hæmostasis, then, varies with the predominance of one or more of these predisposing factors. Why is the loss of such large quantities of blood without material change in the blood-pressure, the pulse-rate, and the respiration possible? It is due to

the normal physiologic factor of safety in the circulatory system. This factor of safety is dependent upon the power of the vasomotor centre automatically to increase its nerve impulses, so that the vascular system as the blood escapes is contracted, thereby maintaining a normal blood-pressure; also upon the rapid transference of fluids from the tissues into the blood-vessels. By reason of this compensation, the circulation through the coronary artery supplying the heart, and through the centres in the medulla, including the vasomotor, the brain, and other parts of the body, is maintained at or near the normal. There are other minor factors in this compensation, which for our present purposes need not be discussed.

There is, then, in hemorrhage a beneficent physiologic circle: namely, an increased vasomotor action sustains the general blood-pressure; hence the circulation of the vasomotor centre is sustained, enabling it to continue its extraordinary work. In time, however, the vasomotor centre and other factors of compensation have reached their maximum effort in vain and the circulation becomes deprived of so much blood that a fall in the blood-pressure results. The circulation through the vasomotor centre is diminished and with it a reduction in the function of this centre, which in turn cannot continue its strong influence upon the blood-vessels, thus permitting a further fall in the blood-pressure, etc. A vicious physiologic circle is then established. Now in surgical shock there is an impairment or breakdown in this same mechanism. If these centres are partially impaired by shock, hemorrhage is obviously less well borne. Conversely, if these centres are taxed to maintain the blood-pressure to compensate for blood loss, shock is less well borne.

It is abundantly established both experimentally and clinically that the combination of shock and hemorrhage is most disastrous. It is not well to take the position that the loss of blood is of little consequence because it may be reproduced in a few days, for the patient may never live to see those few days; his death may be due to the want of blood that was heedlessly lost. The factor of hemorrhage is a most important one viewed

from every standpoint, for the safety of the patient, the better execution of the precise technic, the training of the surgeon, and the maintaining of operative ideals. The various details of special importance in particular operations will be considered elsewhere.

In the acute pathogenic infections there is a pathologic increase in the arterial blood-pressure. In some other acute infections, notably typhoid, there is a pathologic decrease in the blood-pressure. The full, high-tensioned pulse of an acute infection by no means warrants the inference that the patient will well endure shock-producing operations. The vasomotor centres are seriously overworked in addition to their being poisoned, and, therefore, have a smaller range of potential power than normal, thus leaving a smaller margin for emergencies. The vital margin of safety is, therefore, diminished in acute pyogenic infections.

THE OPERATIVE TECHNIC IN RELATION TO PREVENTION OF SHOCK.

It may be accepted as proved that the traumatic factor, as opposed to the psychic and predisposing factors, may be accurately measured in physiologic values. Traumatic shock is due to the mechanical excitation of nerve-tissues. Each contact produces an effect in direct ratio to the number of nerve-fibres or nerve-endings involved and to their intensity. The strictly traumatic factor in surgical operations, then, is the sum total of the contacts multiplied by the intensity of application. Prevention lies in minimizing the number and intensity of contacts. Each patient is presumed to have a strictly limited margin of vitality which may with safety be destroyed during operation. A certain responsibility then attaches to each contact. Since the physiologic result of these contacts is subtracted from the available amount, it becomes a question of physics and mathematics to determine how far an operation may be extended. Herein, too, lies the reason for the personal factor of the surgeon. The precise, gentle operator, thoroughly trained to recognize the physiologic values of trauma of the various tissues and organs, will succeed most often in the great hazards of surgery.

REGIONS.

In the application of clinical and experimental research to operations upon the head and neck, separate consideration will be given to anæsthesia and hemorrhage.

In operations upon the brain, venous hemorrhage assumes a greater rôle than arterial. It is obvious, then, since nitrous oxide produces more marked venous congestion, that this anæsthetic is strongly contraindicated. Ether causes less venous congestion than nitrous oxide, but more than chloroform. Were they equally safe, chloroform would have the preference. Unfortunately, chloroform has inherent dangers hitherto uncontrollable. Sir Victor Horsley prefers chloroform anæsthesia, on the ground that in the hands of an expert under his guidance he is able with apparent safety to lower the blood-pressure; hence, minimize the hemorrhage at will. I have verified these observations in the experimental laboratory. The less the hemorrhage, the less the manipulation, the less the shock. Since there are other efficient means of controlling hemorrhage in extracerebral operations, one would here choose the safest anæsthetic, ether. While the skilled anæsthetist may, by the method of Horsley, markedly diminish hemorrhage by a careful manipulation of the anæsthetic, it is also true that expert ether anæsthesia by the open-drop method may likewise greatly diminish venous congestion.

In operations upon the mouth, throat, face, and neck, ether anæsthesia, by tubage of the pharynx through the nares, greatly facilitates the operative technic, the opportunity for the control of hemorrhage, and the maintenance of an even anæsthesia.

Percussion of the brain brings out a physiologic response from the circulation and respiration. The blood-pressure and the respiratory rhythm become uneven. In opening the skull the burr drill and the trephine, therefore, have the preference over the mallet and chisel. In the use of the latter the method of application is a greater factor than with the trephine or drill. If the chisel is sharp and is held at a correct angle and used in the manner of a skilled artisan, driven by light taps, its effects are minimized. The sum total, however, cannot be so

small as the effect of opening the skull by means of the saw or drill.

While these fine distinctions may not be of importance in the average case, in critical ones they become so. In the further cutting of bone, in the fashioning of osteoplastic flaps, the method that offers the least contact with the dura and the least percussion produces the least shock. After the skull is opened and the further technic involves the brain itself, the operative problem becomes the most delicate known to surgery. The rougher methods used in other parts of the body must be discarded. Here every contact counts, and not only every contact, but the intensity of each contact. A slight touch here might set up a greater number of impulses than that of traumatizing the entire nerve-supply of a cross-section of both thighs. Here there is a concentrated opportunity for damage, and here, too, the surgeon must bear in mind constantly the evil effect of contact with the air. One needs only to remember how difficult it is in making electrical stimulations of the cortex to maintain excitability without irritability when the brain is exposed for a few minutes to the air. First there is excitability, then irritability, then no response to stimulation.

In operations for the relief of increased intracranial pressure the life-controlling centres are in the midst of a struggle for functional existence. The blood-pressure may be high. In an increased intracranial tension the bone-encased brain is unable to escape from the direct pressure, except to a limited extent, by the displacement of the cerebrospinal fluid. As Horsley and others have shown, the brain itself is inelastic and incompressible; therefore, when a clot-depressed fracture, an abscess, or a tumor occupies intracranial space, it is first at the expense of the displaced cerebrospinal fluid, then the circulating blood and lymph. Now pressure is exerted in all directions undiminished. Among other portions of the brain whose blood-supply, hence its function, is thus threatened, are the life-controlling centres of the medulla. Nature attempts to meet this emergency by raising the blood-pressure by vasomotor contractions over other areas, especially the splanchnic, thereby

causing a rise in the general blood-pressure, tending to drive back the blood to the anæmic brain. The extent of the increase in the blood-pressure, then, in the presence of an increased intracranial tension, may, in a rough measure, be an index of the height of the intracranial tension. If the intracranial tension rises there comes a time when the margin of physiologic compensation is exceeded, the vasomotor centres yield, the blood-pressure falls, anæmia of the brain is complete, and death follows. It is obvious that when the vasomotor centre is under such stress of over-work, if operative therapy is applied it is vitally important not to reduce the blood-pressure. The blood-pressure may be reduced by the anæsthetic, by shock, or by hemorrhage. If these cases are unconscious, it is by all means the safest to enter and cut away the skull under local anæsthesia. After relief of tension physiologic readjustment may be awaited. It is in this class of cases (to be more fully discussed later) that if the blood-pressure is lowered by anæsthesia, shock, or hemorrhage for a period of a few minutes (six or more) the patient cannot recover. The pulse, the high tension, and the apparently sound circulatory state give no idea of the narrow and dangerous operative margin. In such cases it would be well to fortify the circulation by other efforts at raising the blood-pressure, such as bandaging the extremities and trunk up to the costal borders, the application of the rubber suit under tension, the administration of stimulants, the head-down posture, in order that the blood-pressure may be maintained during the operative manipulation at a sufficient height to insure a safe cerebral circulation. It is well to bear in mind the fact that the higher centres of the brain may be, and probably are, under a stress for the necessary circulation as great and important as the medulla. Other experiments have shown that the brain itself cannot endure complete anæmia beyond six or eight minutes. This is, I believe, the explanation of the sequence after the successful relief of the brain of pathologic tension,—the expected consciousness never returns, and after a few days or weeks the patient succumbs.

In the cases, then, of operation upon the entire group of

increased intracranial tension, the method of procedure should be quite contrary to that of intracranial operations under normal tension.

While the circulation in increased intracranial tension presents problems of such extraordinary delicacy, the respiration must not be forgotten. Long ago Horsley and Spencer showed that in intracranial lesions, such as gunshot wounds, the respirations are more rapidly arrested than the circulation.

Among 105 personal operations upon the brain I have in four instances encountered arrest of respiration. These occurred in the earlier part of the series, when I routinely anæsthetized the patients. In two of these, by maintaining artificial respiration, I was able rapidly to cut away the skull and secure relief to tension, after which normal respirations were resumed. I have not seen a single instance of respiratory failure in such operations since I have taken into account the pathologic physiology above described.

In operations upon the mouth, face, and neck, the shock-producing factors in the main are hemorrhage, anæsthetic accidents, cardio-inhibitory reflexes, and rough contact. We have already sufficiently discussed the avoidance of anæsthetic accidents by tubage of the pharynx, permitting even anæsthesia and preventing inhalation of blood. There are now methods whereby the loss of blood may be so greatly minimized as scarcely to take its place as a factor. This may be done by temporary closure of the carotid artery, head-up posture, and careful dissection after sequestration of blood. By these means the field may be kept free from blood and hence so clear that even the lymphatic vessels may be clearly seen. The prevention of cardio-inhibitory reflexes, which may occur as a result of traumatism of the superior laryngeal nerve, the vagus, or the laryngeal mucosa, may be obviated by a preliminary hypodermic injection of atropine, by the cocainization of the laryngeal mucosa or the superior laryngeal nerve trunk, and as far as possible by avoiding contact. Sharp dissection, minimum retraction, and sponge contact have happily reduced the rough contact of the past, in which the maxilla was evulsed by brutal

mechanism for the extraction of a tooth. I have not seen a single case of death from shock in the last three hundred operations on the face and neck.

Operations on the larynx, by reason of the rich supply of inhibitory terminals of the superior laryngeal nerve, present special problems. Intubation, laryngotomy for foreign bodies, intralaryngeal manipulations, or laryngectomies, may be done without risk of collapse provided a sufficient dose of atropine be previously given, and provided further that the laryngeal mucosa be cocainized. In laryngotomy (an operation to be avoided as far as possible), after the incision has been carried through the cartilage to the mucosa the latter may be readily cocainized by means of a hypodermic syringe along the entire line of the proposed opening. The larynx may then be entered without producing cough or even an altered respiratory rhythm. Through this opening, then, the laryngeal mucosa may be cocainized by spray or swab and a quiescent larynx obtained.

Some years ago, while interested in intubation for laryngeal stenosis in diphtheria, I encountered cases of sudden collapse with arrest of respiration. I at first erroneously supposed it to be obstruction due to forcing membranes down ahead of the tube. In my efforts to extract the supposedly obstructing membranes I made death doubly sure.

Upon investigating this subject in the laboratory it was at once observed that, (1) reflex inhibitions could account for all the symptoms, and that (2) the respiratory mechanism never yields instantly to obstruction but makes a struggle with increasing respiratory force, bringing into play all the extraordinary muscles of respiration until either the obstruction is overcome or death ends it. At a later time I was able to verify in two cases the correctness of this view as follows: Children in desperate straits were intubated as quickly as possible. Sudden collapse with failure of respiration and disappearance of the pulse from the wrist quickly followed. These children were at once inverted, head down, with their backs resting against my knees, an assistant holding their feet, while I pressed rhythmically and rapidly upon the thorax over the

heart. There quickly appeared a slow cardiac rhythm, gradually becoming more rapid, finally reaching a safe status, followed by spontaneous respiration and complete recovery. In 210 intubations I encountered but two deaths from reflex inhibition and a number of temporary depressions, all clearly due to the direct stimulation of the terminals of the superior laryngeal nerve and the larynx. Had I thus understood the cause they could have been prevented. Nerve-endings having the power of producing inhibition are by no means confined to the laryngeal mucosa. The rima glottidis is also sensitive and may respond to such impulses. The posterior nares, though to a less degree, may exhibit such responses to trauma. In operations for adenoids these reflexes should be borne in mind. I have no doubt that sudden depressions occasionally attributed to the anæsthetic were in fact reflex inhibitions from the operative trauma. In performing these operations I always cocainize the pharynx and give a preliminary injection of atropine.

Thorax.—But little need be said on the prevention of shock in operations upon the thoracic wall, as the problem here is covered by general principles. However, in operations within the thorax, the problem becomes more specialized. In empyema, in hemorrhage into the pleura, in large transfusions, it is well to bear in mind that in removing the pressure, the flow of blood in the large vascular trunks, notably the veins, is subjected to a great interference, resulting sometimes in acute dilatation of the heart. This is, I believe, not usually recognized. The sudden heart failure or collapse that has been attributed to that vague etiological factor described as a displacement of the heart, or the heart shifting its place, is probably a question of an acutely dilated heart. In many of these cases the heart is already overtaxed and its muscles poorly nourished either by poisoned blood or by insufficient blood. The gradual reaction of increased intrathoracic pressure is a line of safety. Manipulation within the chest causes many important changes in the respiration and the circulation, and operations in this field must, for the present at least, be most carefully planned.

Abdomen.—Every contact with the parietal or visceral peritoneum acts as a shock factor; contact with the omentum, on the contrary, causes no fall in the blood-pressure. The upper part of the abdomen is more shock-producing than the lower. It is needless here to refer to the necessity for precision and gentleness. In the routine operations but little shock is seen in the good clinics of the world; but in acute, or in chronic infections, when the patient is toxic or greatly reduced, the problem does become an acute one. In acute infection with abscess in the peritoneum, the gall-bladder, or the kidney, nitrous oxide anæsthesia, while not so satisfactory to the surgeon, is far safer for the patient. In abdominal operations it is well still to call attention to the necessity of protecting the viscera as far as possible from the air. Unless contraindicated, a hypodermic of morphine in extensive intra-abdominal operations is of benefit, first, because of the splendid relaxation; second, because less anæsthetic will be required; third, because the psychic factor is diminished. I think my surgical colleagues will agree that among other good results that have followed increasing experience in abdominal surgery is the almost complete disappearance of postoperative obstruction, once supposed to be so materially promoted by morphine, even when morphine by the same surgeon was given as a remedy for mechanical obstruction. In anæmic, emaciated, hence poor, surgical risks; in long-continued suppurations, in which it is apparent that if surgical relief is not obtained the patient will die, while it seems equally certain that if the effort is made he will die,—in these cases I have found that, happily, the direct transfusion of blood will so much exalt the general vitality and strengthen the circulation as to convert these risks into relatively safe cases.

In operations upon the extremities I have substituted progressive hæmostasis for tourniquets. An amputation is performed by precisely the same rules of dissection as excision of the breast. The nerve-trunks are blocked by injecting cocaine before dividing them. In amputation of the arm or shoulder the brachial plexus is first exposed and blocked with cocaine.

No shock whatever then attends the operation, at least none until the cocaine effect wears off. In senile gangrene, requiring amputation of the thigh, I use precisely the same instruments as in excision of the breast, except for the addition of the Gigli saw. The operative trauma is spread evenly over about twenty minutes so as not to overwhelm the nerve-vascular system by a flood of stimuli in a short period. The total amount of blood lost is, by this method, diminished, as the vasomotor oozing is entirely obviated.

ON THE TREATMENT OF TRAUMATIC SHOCK.

The depression in the majority of the traumatic cases is due to both shock and hemorrhage. In the absence of a clear history it is not easy to determine their relative importance. Fortunately, the treatment of each is virtually the same. In traumatic cases demanding operation, should one operate immediately or should one wait for reaction? In my judgment the question may be answered either way. Immediate operation may be performed if the operative field can be blocked by cocaine, thus preventing further shock, as, for example, the lower extremities by spinal anæsthesia, the arm by blocking the brachial plexus, or if, as will be later explained, the patient is treated by a transfusion of blood. On the other hand, if these circumstances do not exist, it is, in my opinion, better to await reaction. At all events, while operating on such cases, the nerve-trunks supplying the field in question should, whenever possible, be blocked, even when general anæsthesia is administered. In these cases, in which sensitive tissue in quantities is mangled, especially in the compound fractures, when the soft parts are no longer supported, the greatest gentleness must be exercised.

Collapse.—While we believe that there should be a distinction made between collapse and shock, this distinction in practice is frequently not recognized. We will consider the treatment of collapse.

The principal causes of collapse coming to the attention of the surgeon are anæsthetic accidents, asphyxia, reflex inhibition, and hemorrhage.

The consideration of collapse presupposes cases of suspended animation. As we soon shall see, we must also consider resuscitation of parts of the brain.

Total anæmia of certain essential parts of the central nervous system is safely endured but little beyond six minutes. There is a marked difference in the length of time that the various tissues and organs of the body can endure total anæmia with safety. The bones, tendons, skin, muscles, the cardiovascular system, the various organs and glands, and the central nervous system show an individual resistance to anæmia. The excised heart, for example, may be made to beat after isolation for forty-eight hours. We are, however, more particularly concerned with the central nervous system in its bearing upon the anæmia of collapse.

In a research made by Dr. Dolley and myself, we found that animals whose animation was suspended by asphyxia or by anæsthesia and then resuscitated at various intervals of time, from one minute up to twenty, showed clearly the susceptibility of the various parts of the central nervous system. We made absolutely certain that there was no circulation and then resuscitation was accomplished by the combined effects of the infusion of Locke's, Ringer's or normal salt solution into an artery, directing the stream toward the heart, by the immediate injection of adrenalin into the rubber tube near the cannula by means of a hypodermic syringe, by rhythmic pressure upon the chest over the heart, and by artificial respiration. By these methods oxygenated blood, with a pressure of from 40 to 60 mm. mercury, was made to circulate through the coronary artery, which caused resumption of the cardiac beat. Following this, in the favorable cases, there was a resumption of the functions of the various organs of the entire body. The return of these functions varied considerably. The description of these phenomena, although of great interest, would, for our present purpose, carry us too far afield. It is sufficient to say that up to six minutes the central nervous system in almost every instance regained its normal functions. The proportion of failures of the restoration of the entire central nervous system to resume

its normal functions after six minutes rose rapidly; and after seven minutes in but few instances was there a resumption of function; after eight minutes resumption was very rare, and in no instance after ten minutes.

For our present purpose we will consider only the respiratory centres, the vasomotor centres, and that part of the brain presiding over conscious or psychic life. The central nervous system of younger animals endures anæmia better than that of the older. Of all the functions of the central nervous system, that of respiration is most persistent; moderate respiratory action of this centre was obtained after as long as forty minutes of suspended animation from total anæmia. The vasomotor centre was frequently resuscitated after fifteen minutes, occasionally after eighteen, once after twenty, and once, in a puppy, after thirty minutes; but that part of the brain presiding over conscious life (the psychic and mental state) was in no instance resuscitated after total anæmia of eight minutes, but always after four. We kept animals for one or two months whose hearing, sight, smell, cerebration, and consciousness were lost. May this not have a practical bearing in the consideration of shock and hemorrhage in the presence of increased intracranial pressure? Who has not operated upon cases of increased intracranial pressure due to hemorrhage, tumor, or abscess and found that while entirely successful in safely relieving the pressure, consciousness never returned? In these cases, if the patient before the operation was totally unconscious, we do not know but that an essential part of the brain had been already subjected to a total anæmia of six minutes or more and that at the time of operation no possible chance of cure existed. The operator, therefore, may never precisely know whether or not the fatal result was due to operation. In another group of cases he may fairly well assume his responsibility, viz., those cases in which there is at the time of operation a high degree of increased intracranial tension but the patient is still dimly conscious. If the patient never regains consciousness following operation in such a case, it is fair to presume that during operation, as a consequence of the anæsthetic, of the shock, of hemor-

rhage, of the posture of the patient, or of all combined, the slight margin of circulation supplied to the brain, giving it its flicker of function, was lost for six minutes or more.

If these conclusions are correct, then in such cases of an increased intracranial pressure every effort should be made not only to sustain, but, if possible, to increase, the general blood-pressure so as to make certain of the necessary circulation during the entire operation. Shock and hemorrhage here have a specialized significance.

ON TRANSFUSION OF BLOOD IN THE PREVENTION AND TREATMENT OF SHOCK.

As a result of experiments on over-transfusion, we found that if transferred rapidly, that is, by a full-head stream from the carotid artery of the donor into the jugular vein of the recipient, an œdema of the lungs followed in some instances. In one experiment, within four minutes after starting the flow from the large donor, froth and serum rapidly poured out of the nose and mouth of the small recipient. On the other hand, when the over-transfusion was done more slowly so as not to embarrass the right heart and the pulmonary circulation, a huge donor and diminutive recipient being utilized, the blood was successfully transferred from the pulmonary to the systemic circulation, the abdomen in time becoming enlarged and gradually increasing until it became so tense that the diaphragm and movable ribs were immobilized and the animal died of asphyxia. The autopsy findings proved that both the liver and the spleen may be ruptured by excessive transfusion.

Transfusion in the normal animal caused an immediate rise in the blood-pressure. This rise continued until from 15 to 110 mm. mercury had been gained. After the maximum had been reached there was usually a decline, though the pressure as a rule remained higher than normal. This was in direct contrast with the effect of intravenous infusion of normal saline solution, which we found to be capable of raising the pressure of a normal animal but a few millimetres mercury, even when the solution was infused from a high column, through a large

tube, under a strong head pressure. Whereas normal salt solution will not sustain the blood-pressure at a higher level than normal, direct transfusion of blood usually does. It was found that at death an over-transfused animal showed a residual pressure of from 15 to 30 mm. mercury. It was also found that animals recently killed, then subjected to a transfusion, may exhibit a rise in carotid pressure as high as 60 mm. mercury. This contrasts with the rise under parallel conditions of 10 to 15 mm. mercury by saline infusion. Blood transfusion exerts a greater influence upon the blood-pressure than saline infusion.

After having found that the blood of normal animals of the same species is physiologically interchangeable; that the blood-pressure may, in the normal animal, be raised and sustained; that if the transfusion be given with too great rapidity the pulmonary circulation may be so embarrassed as to precipitate an acute and even fatal œdema of the lungs; that if the transfusion is given more slowly the blood may be transferred from the pulmonary to the systemic circulation in safety; that an excessive transfusion thus given may cause serious damage to the abdominal viscera, even causing immediate death; and after having established a safe technic and the limits of safety, we then experimentally inquired whether or not, by the transfusion of blood, its volume may be sufficiently increased to fill up the relaxed vascular system, to cause more blood to reach the heart, and so increase the outflowing stream, hence, help to overcome the cerebral anæmia of shock, which in turn would be followed by an increased activity of the vital centres, thus supplanting the vicious circle of anæmia by the beneficent circle of hyperæmia.

It was shown experimentally that the influence of transfusion upon the blood-pressure in every grade of shock was sufficient to raise it, frequently to the normal, occasionally even above it, and to sustain it so for at least a number of hours.

After the striking effects of transfusion in the treatment of shock were fully established, we undertook another series of experiments to determine what effect, if any, a careful overtransfusion in the normal animal might have in the prevention of

shock. It was found that animals carefully over-transfused so as not to embarrass the pulmonary circulation on the one hand, or over-charge the abdominal viscera on the other, then subjected to shock-producing procedures, could not be killed by shock alone. The blood-pressure could be reduced to a certain degree, lower than which, by trauma alone, it was not possible to reduce it.

Extending our experiments, we found that traumatizing the spinal cord produced either a rise or no material effect. We then destroyed the medulla, after which, by maintaining artificial respiration, the circulation still went on. We then made the supreme test of decapitating such over-transfused animals, and found that the blood pressure was still evenly sustained without other assistance than artificial respiration. Even when respirations were not given, the height of the pressure was not changed until affected by asphyxia. One animal lived for over three hours by merely keeping up artificial respiration. This remarkable circulatory state is readily understood by considering for a moment the physiology of the heart-beat. The heart may be removed and kept on ice for a day or more, then, if oxygenated, defibrinated blood under pressure of from 80 to 100 mm. mercury be circulated through the coronary vessels, it will beat again and continue to beat for a number of hours. Even a coronary pressure raised to that height by metallic mercury may cause the inauguration of the heart-beat. Now in the over-transfused animal the vascular system may be so filled with blood that its elasticity is utilized to create a resistance against which the heart may act, resulting in a pressure of from 80 to 140 mm. mercury in the aorta, hence, in the coronary artery. There is no reason why, therefore, the heart should stop beating so long as the elasticity of the vessels gives the necessary resistance, despite the loss of the head.

It is perfectly obvious that in utilizing a transfusion of blood for the purpose of establishing a static circulation, the heart must be equal to its good share of the work. In the senile heart, in myocarditis, in essential heart lesions, an acute dilatation or paralysis of the heart or pulmonary œdema might

occur. Our experimental evidence refers only to the normal heart.

In the clinical cases of uncomplicated shock treated by transfusion the symptoms of shock disappeared in a manner so remarkable as to suggest its being a specific treatment. Equally successful were the preliminary transfusions in cases that for one reason or another were in such a low vital state as to appear to be unable to endure the necessary surgical technic. This was especially true in the cases in which hemorrhage was the important factor in producing such depressed vitality. Thanks to transfusion the yesterday of our lost opportunity may be reclaimed.

ON THE TRAIL OF THE SUBCONSCIOUS *

JOSEPH JASTROW, Ph.D.,
Professor of Psychology in the University of Wisconsin.

THE pursuits of the physician and of the psychologist, primitively the same because neither had as yet come to his own, have in turn become divergent, at times distantly parallel, and more recently convergent to a common direction, united in sympathy of purpose. The bond of their kinship, and equally the source of their contention, is the attitude each is called upon to assume toward the evasive but persistent claims of consciousness,—at one period condescendingly recognized as a troublesome poor relation, at another welcomed as next of kin; now its legitimacy under vague suspicion, and again heralded as the foremost heir of the estate. Truly the vicissitudes of the family affairs of body and mind offer material for most interesting memoirs. Yet the branch of the house from which we of to-day claim descent, at least as a clan of prominence, is not a very ancient one. It dates, it is true, from the period of the intellectual conquest, when old knowledge was made new, and the revolution from the feudal systems of the mind had brought rapidly forward the vigorous advances of a fresh touch with nature. The understanding thus furthered remains the basis of an increasingly appreciative intercourse between the practitioner and the mental analyst, the latter now making his advances through the findings and the training of the laboratory, the former through a common diagnostic temperament alert to the subtle intrusions of a psychic complexity. Yet the present purpose does not demand a retrospective accounting. It assumes the less formal aspect of a visit from one branch of the family to another, the delegate encouraged by kindly invitation to recount some plain tales from the hills of his fre-

* Lecture delivered February 8, 1908.

quent sojourn, some comments upon the problems of his calling and their bearing upon the allied interests of his medical cousins.

The task which the psychologist assumes, not hastily but deliberately—while yet he appreciates the wise caution of the physician who fears to tread beyond the portals of a clinical experience—is to set forth the part of consciousness in the drama of life, the incidents and accidents of its career, and to essay some interpretation of its composite character. In this procedure he begins by noting how the functional utility of consciousness is guaranteed by its very establishment, and is step by step sanctioned by a progressive elaboration in the evolutionary series. I cannot doubt that I am more elaborately aware of myself and my world and more subtly reflective upon its revelations than is the dog who shares my hearth, however much the acuteness of his perceptions and the sober pursuit of his purposes excite my admiration. And if from my philosophic window I look out upon the laborer who with his companions is digging in the street and consider how much more complex are my mental processes than his, my complacency may find a check in the thought that possibly my gently bred companion in his own inarticulate impressionism may be indulging in equally impertinent appraisal of himself and the homeless cur outside. In both cases the contrast, judged by nature's catholic canons, is of a wholly subordinate import. What we share with one another in our common humanity is indefinitely more comprehensive than the deviations of our personalities; though it is just these secondary variations that for many of us constitute all that makes life worth while, and which very properly will loom large in later vistas of our excursions.

The utility of consciousness is readily appreciated. It is obvious that functions on the whole achieve the breadth and depth of awareness which their efficiency requires. The sweep and the brilliancy of the search-light of attention varies constantly with the voltage of the interest with which we keep alive the strands of our connections with the outer, and still more significantly, with the inner world. (Let me add parentheti-

cally that it is mainly with the induced currents of the mental system that I am to deal.) In healthy organisms attention goes where it is needed; and we go about our life's occupation, not with the meddlesome curiosity of busybodies, but with the poise and directness of thoughtful purpose. Circulation, respiration, secretion, and that troublesome and by no means always silent partner in the concern—digestion—pursue the even tenor of their several ways, while concordantly the delicate balance of tensions, impulses, embryonic and decadent metabolism of the nervous traffic is ever operative to shape the tone of our well-being, the temper of our moods, the profit of our central pursuit. Likewise it is well to remember that the mind as the body, though with a very different economy, has a normal temperature. We cannot maintain the red glow of the mental forge for more than brief periods, and only the more fortunately endowed in occasional moments reach the white heat of inspiration. For the most part an underglow of flickering combustion goes on with now and then a spark, and more frequently the peaceful embers of an unreplenished hearth. The normal mental temperature is compatible with, indeed requires, long periods of commonplace pulsations, not notably interesting, but natural withal. Likewise is it the case that much of this mental industry is of the nature of the idle singing of an empty day. When distinctive and imaginatively maintained upon somewhat higher than the ordinary level, we call it revery, or day-dreaming, or when vaguely shrouded in the forms of hope or longing and suffused with the privilege of the male sex, pipe dreams. Mental loafing it might well be called for plodder and genius alike. This normal gait of the dray horse—and other's stables are full of them, however blue-ribboned the steeds that bear our livery—is a prosaic but important expression of the mental procedure. Much of the business of consciousness is lowly. The butcher and the baker, if no longer the candlestick-maker, set out upon their daily and necessary rounds. It is a monstrous perversion of that fitting Hellenic term to count as psychic only the accentuated or aberrant or startling productions of the mind's activity. We are all of us psychic through and through, even as we

get up and as we lie down. Thoroughly if commonplacely is our living impregnated with all sorts and conditions of consciousness, bright and dull, deep and shallow, lofty and lowly, fluctuating ever but rarely quiescent.

Let this impressionistic sketch suffice to recall the comprehensive functions of consciousness in the human economy. But clearly also man was not meant to live by consciousness alone. Much of his activity is provided for by a foreseeing nature that guides his impulses encouragingly to their fulfillment, and leaves to his conscious self but the decisive direction of their maturing. And in large measure the genus homo follows in the footsteps of his preceptress and acquires a comprehensive and miscellaneous stock of second-nature habits, that mark the issues of his experience and education. Thus once more, he learns to conduct his mental affairs with much dependence upon personally trained subordinates and understudies, who enter upon their proper cues and take their parts unobtrusively while the leading lady or the leading gentleman rises to the occasion—or to the gallery. Each one of us is not only a player and the world his stage, but a stock company with an extensive even if not brilliant répertoire.

The course of events would move smoothly enough—and incidentally life would lose much of its charm as well as of its comedies and tragedies—were consciousness always wisely directed. "The ideal man" (I am indulging in the literary privilege of citing from my own pages) "might be said to have no forms of awareness but useful ones. But so long as it is human to err, the exhibition of various failings in the manner of our consciousness will remain characteristic of our psychological make-up. So long as the manner and degree of the conscious direction of our actions may vary, it follows that such direction may be wisely or unwisely, helpfully or disturbingly applied." The natural history of consciousness is vastly enlarged by the inclusion of its pathological vicissitudes. Notably is this true of those subsidiary and suppressed participations of consciousness upon whose trail we are set. The false distribution of consciousness is most simply illustrated in

such ordinary observations as the difficulty that besets many a person for whom a pill, not necessarily a bitter one, has been prescribed. When one tries to perform by intent and attention what is naturally a subconscious function, entanglement results. It is said that in China the swallowing test was used as an ordeal among suspects to reveal by the embarrassment of a subconscious function the perturbation of a guilty conscience. The test was quite as likely to reveal the most nervously disposed individuals. An interesting illustration of the principle appears in the recognizable disparity between the stage cough or laugh and the same simple reactions performed in response to natural stimulation; or once more in the hollow cordiality that social custom entails, and the versatile mockeries of affectation. Insincerity to the discerning rings false. The counterfeit may approach the genuine with embarrassing resemblance; and yet the expert sensibility sharpened by an intense interest in human character, suspects, examines and detects. What is pertinent is that the revelation of the disguise is frequently in terms of the failure of consciousness to manage what is by right or in part a subconscious affair.

The present purpose is predominantly a practical one: to present what the pragmatist terms an efficient conception of subconscious functioning, and to reach this end by way of a survey of mental abnormality through intrusion of subconscious activities. Thought reaches its distinctive phase by assumption of a logically directive purpose. Thinking readily assumes even in the thoughtful, the form of an effort, a task. Its more easy-going progress, as already indicated, is an idle musing, not a brisk and straight trot, but an easy stroll or ramble. The present thesis emphasizes that a release of guiding tension throws the mental movement back upon this logic-forsaking mood. Dreaming presents this relation; so do the lighter stages of anæsthesia (ether or nitrous oxide gas); so does the selective action of a psychic poison, from alcohol to opium, to hasheesh, or mescal. The thought-movement of these states—provided that the mental wave is not sunk below reportable level—reflects the stuff that dreams are made of. It is

by no means all chaos; much of it is in the nature of the communing of the private self, playful it may be and yet significant. Consider how utterly impossible it is to lay bare unreservedly the reflections, impulses and longings of even the purest and simplest soul. Now and then the sympathetic physician in the consulting confessional has revealed to him some glimpses of the inner life, usually closely screened, often unacknowledged or suppressed, at times entertained—angel and devil alike—unawares. And the very act of confession may purge the troubled soul by making explicit and accessible what was evasively taking shelter in subconscious retirement. An absolutely, painfully faithful mental autobiography might well read like a "case" for the psychiatrist. Hence once more let it be noted that this sort of half-dramatic entertainment of suppressed and inchoate dream-stuff is present in great profusion, and may under release of tension, under marked stress, under hereditary flaw, press forward to disturbing, even to dominant expression; second, that a vital factor in all work, all purposeful thought, all expression and significant behavior, certainly in all public appearance under the management of the social self, is direction, control, selection and repression, with the reins in the hands of the preferred self.

A corollary from this principle takes us directly to the hearth of the mental habitation, to that aspect or maturing product of consciousness, which we call self-consciousness. It reminds us that the self that we actually are is many-faced, showing one visage to the formal public, another to the professional colleagues, a third to the family intimates, and yet others at home and abroad, in mart and forum, in club or field. Biographers at times present as diverse views of the characters of their heroes as do artists of their outer lineaments; yet each may be truthful. We are not Jekylls and Hydes, nor even unduly *poseurs;* but our personalities are complex and versatile. The abandonment of long-sustained ideals, the release of struggle, or the stress of a primeval emergency loosens the veneer, even though it may be both thick and adhesive, and reveals the plainer, more natural grain beneath. And at times

what a welcome relief to don the *negligée* self, and within the privacy of four walls relax and yield to what we naturally are! The strenuous life is not a matter of brawn and bustle; the real strain is the mental one of striving for a part a little beyond attainment of struggling ambition, and troubled unrest. And in the end, the self that he becomes when a man comes to his own, is a selective maturing, by successive shedding of shells outgrown, of the individuality chosen by combination of circumstances and endowment, from among the possible selves that he might have developed. Yet these suppressed potentialities are not altogether disowned and may yield evidence of a cloistered existence, by occasionally breaking through their wonted confines.

The next stage of the inquiry concerns the character of the growth and acquisitions of the self that is chosen from among the many called. By what tokens is the legitimacy of the self's qualities and belongings recognized and acknowledged? There cluster about the full-fledged, personally conducted, psychic procedure three overlapping and interpenetrating qualities or privileges: for the first you are asked to accept the term incorporation. I incorporate into my personal experience in a sense everything to which I give attention, all that the attending ego accepts. I know of course that I do not respond to a small fraction of all the multitudinous sense-appeals that bombard my senses. To maintain any singleness of purpose in this tumultuous world my mind must turn its deaf ear to these distracting bids for attention, and be not at home to a further range of calls, pleasant and unpleasant. For the most part this is easy under normal health, freedom from care, and in customary surroundings, where only the unusual sounds an alarm. Moreover, I cultivate a concentrative power, enforced by a sense of duty, ambition, love of my work, or what not; and this holds me to my task. But, assuming a lull in the day's occupation, I am fairly accessible to a varied range of claimants, but give to each no more than the nod of assent, the moment of recognition sufficient to its incorporation with the stream of my mental world. The bodily economy is insistent;

and nature's cries in feelings of unease or ache or tension may well be, and usually are needed. My routine is facilitated by well-organized habits; the shaping of the letters as I write is taken care of while I devote my major attention to what I wish to say. All this is familiar and normal. But what happens when my incorporating privileges are curtailed, and how do they come to be curtailed? Here the subconscious enters; or rather it is present throughout, only a shifting of its mode of coming on seems to disclose it in a new and more striking rôle. Absent-mindedness is the popular and instructive index of the situation. I have been troubled all day because I have mislaid a bunch of keys. I know that I disposed of them but cannot recall place or occasion. I put them away while my more active attention was otherwise engaged, and the subconscious phase of my mental concern, that did the business, will not reveal to me where the keys are. I shall either find them by chance, or I may succeed eventually in tracking the trail of my subconscious understudy, who is a very near relative of mine and shares many of my habits. My friend who in similar manner mislaid a notebook was very neatly furnished with the successful associative clue. The telephone bell rang; and instantly there came the conviction that yesterday a similar call was answered with notebook in hand, and that the book would be found, as it was, on the telephone shelf. Likewise have I friends who leave umbrellas on shop-counters, and when a subconscious impression nudges them and reminds them that a moment ago they were carrying something in the hand, they try but fail to recall what it may have been. And my friends have friends who actually walk home in the rain with an umbrella neatly rolled under the arm, while they berate their imprudence in not providing themselves with this useful but memory-taxing protection.

The symptom thus indicating a lapse of incorporation is properly termed an anæsthesia of a mental type. It is normal enough when applied to the lesser concerns of life and when easily corrected. It is abnormal when the lapse is persistent, or systematized or peculiarly induced. The hysterical anæs-

thesias form the classical example, more convincing than any experiment the psychologist might arrange. A patient has an anæsthetic hand, whose welfare has vanished from the concern of her central self; you may pinch, burn or abuse this marooned member, and there is no pain or protest. Incredible as it seems at first blush, it is yet the fact that her abnormality has led her to neglect to incorporate that hand within the scope of her self feelings. What is central to our purpose is that some suppressed type of registry of the hand's experiences does take place, just as there is some latent impression of the mislaid notebook, or of the much desired umbrella. The sound of the telephone bell taps the subconscious source; and if I were to jostle the umbrella under the arm of the distract individual he would instantly come to and recognize the situation and the umbrella. But the hysterical exclusion from consciousness is for the time persistent and abnormal; and I must have recourse to strategy to circumvent it. I pretend that I am a mind-reader, and ask the hysterical subject to think of a number, and while she is doing so, I tap seven times upon the anæsthetic hand. When I anounce that she is thinking of the number seven, she is surprised at my expertness, and does not realize that the suggestion has come to her from a disowned subconscious source.

The hypnotic state similarly distorts the incorporative privilege; and at my bidding, the subject's hand becomes insensitive, or his eyes blind, and his ears deaf, to such selected areas of impression as I choose. Yet the unfelt touch is subconsciously registered; the sound is not wholly lost, the vision not wholly out of range. I circumvent the anæsthesia by artifice or by antagonistic suggestion, and obtain proof as before, of the suppressed incorporation. To illustrate: I arouse the hallucination that a lion, gentle and well-bred, is in the room. My subject sees the creature, describes its appearance and movements, adding a gratuitous touch or two from his own fancy, and as usual upon awakening disclaims all knowledge of the adventure. But before restoring him to normal consciousness, I have implanted in his mind the suggestion that if (when he comes to)

the wedding-march is heard he will see something unusual when he gazes into a glass of water. Presently by arrangement the familiar strain is sounded and he describes the reflection of a lion in the mirrored surface. Or, if my subject is equal thereto, I ask him when awake to draw any animal he chooses; and unsuspectingly he draws a lion. Yet again: I impose not an hallucination but a mental anæsthesia. I cause him to be blind to the letter *a*, and thereby reduce such a phrase as "alabaster from Madagascar" to an unpronounceable jumble of consonants. Yet obviously he must see the "a's" to avoid pronouncing or writing just this specified and no other element of the alphabet. In all this the hypnotic assimilation is conditioned by the channels of my suggestion, thereby indicating in what manner the incorporation is handicapped; while its paradoxical mode of revealing what the normal consciousness claims not to know, not wholly unlike the status of my lady who in cutting a too presuming acquaintance describes the variety of discomfiture exhibited by the person whom she did not see—is typical of the abnormal mode of participation in the subconscious registry.

Orientation is the second and essential aspect of the developed psychic procedure. It presents the psychological bookmark whereby we note the successive moments of life's unfoldment. Its service is concretely illustrated in the coming to after the minute's loss of consciousness under nitrous oxide gas, when articulately or by expression the patient asks, "Where am I?" It is quite as explicit in the recall of the hypnotized subject from the realm of bizarre suggestion to actuality, or in the sudden awakening from dreamland to the same old world, which is the normal clearing-house through which we certify the validity of the psychological currency. Not only is there orientation to the familiar landmarks of our environment, but to the still more familiar set of feelings that compose so evasively the essence of our personality. One phase of my activity ever keeps tab of time and situation and reminds me at intervals that I must not write too long; for I have a class to enlighten later in the morning. Likewise a summons from that insistent discourager of leisure—the telephone—may unpleasantly break

through my absorption. Or again, I may lose myself at the theatre and realize only the stage and the predicament of the hero: while the fall of the curtain shuts off the one and sends me back to the other world. Yet my suburbanite neighbor was fidgety at the very climax because his subconscious mentor kept nagging him to be sure not to miss the 11:10.

The specific product of a disturbed orientation is an hallucination. The dream so long as I sleep is to me the keenest reality; for I have wholly forsaken allegiance to the world in which I pay my bills, to its obligations, to its physics and biology and psychology. I fly, and am ten feet tall, and see through stone walls, and peer through mysteries by the exercise of powers compared to which telepathy is as simple as looking up the answers in the book. Yet some allegiance to a logic-bound cosmos remains, and fitfully or persistently asserts itself. All this seems normal enough; it is not so much the forsaken as it is the handicapped or wrecked orientation that makes the impression of the abnormal. The hypnotized subject maintains some sort of orientation towards the objects about him; but the interpretation thereof is distorted by my suggestions. He accepts my fountain pen as a stiletto and the upholstered chair as his kneeling victim. Or, if I choose, I summon equally well out of thin air fictitious appearances whose invisible form he sees with his mind's eye, whose voices he hears and whose messages he interprets according to my suggestions so far as I intrude them, by his own endowment and training for the rest. Yet, as before, I can secure evidence that some phase of his handicapped mentality recognizes the artifice of the situation. Similarly the hysterically constructed world presents hallucinations that border puzzlingly upon fabrication, because the orientation is so subtly impaired. The trance state is variable by reason of just this fluctuation in the loss of orientation. It is entered as a rule, just as we invite sleep, by a consenting direction of the mind; and the pronouncements of those who enter this state for the purpose of impressing their friends or clients with the strangeness of their powers, disclose a partial orientation to the surroundings, and in some measure a draught

upon mental resources that do not yield to direct voluntary appeal. Many of the mistakes of the older students of hypnotic phenomena were due to their failure to recognize that their subjects maintained a *partial* orientation to the environment, and from what they heard or saw, derived suggestions which they elaborated to make the results accord with the expectations of the experimenters.

It is the distinction that we are now drawing that offers the popular line of demarcation between sanity and insanity. Unless I can hold apart the world of fancy from the world of fact, unless I distinguish between what I have dreamed or romanced and what I have experienced, I cannot square my doings with those of others or with the great world without. It is just because these obligations are so slightingly treated by the eccentric and the inhabitants of the psychopathic borderland that we find amongst them such glorious liars. We conclude that hallucinations are of all sorts and degrees of reality and unreality, because they play in and out of the subjective and the objective world; and they are such in part by reason of a subtly subconscious prompting of the hallucination, and again by virtue of a subconscious recognition of the fiction. We observe likewise that something like this is what is meant by liability to suggestion, a tendency to forsake the critical tests of reality, to fall back to a curtailed privilege of orientation. The process fortunately works both ways; and in many cases,—as the psychic treatment of mental disorder shows,—we can suggest patients out of their perversities as effectively as their aberrations suggest them into the abnormal attitude.

The third and consummating privilege of a rounded psychological status is initiative. The sense of initiative appears with the feeling of intention, the merging of deliberation into impulse, and the passage of impulse into performance. The feeling is rendered more vivid by the presence of obstacle or difficulty. When things sail along smoothly and fluently and production is easy, the sense of initiative is lightened. Relieve it still more by an unusually happy support of the associative mechanism, and one may pass to the feeling of its entire abey-

ance—an impression illusory in fact though convincing to the subject thereof—as though the result were produced by an extraneous agency, or, in the loftier formulation, by gift of the muses. The factor of initiative is somewhat complex; and if you will pardon a brief lapse into the *ex cathedra* habits enforced by a score of years, let me set forth that it presents a "firstly" and a "secondly,"—an awareness connected with the accumulation and escape of the puff of mental energy necessary to the performance, and then a return message from the muscles to the effect that the deed is done. Impairment of initiative is accordingly of several types, and at the briefest—all still within the normal range—(1) a lapse of outgoing awareness, so that we do things without knowing it but are aroused to the consciousness of the action performed through the aforesaid return sensations; (2) the presence of the feeling of preparatory initiative, but a consequent falling out of mind of the return report; and (3) the running through of the entire procedure without arousing awareness at either end. Moreover, the formula must be modified to include the more subtle aspects of mental effort, the inner conflict with but slight motor issue; for throughout must we bear in mind that repression is just as typically action as positive performance; that conflict of impulses, the holding down of native tendencies, and all that is meant by inhibition, is as elaborately and effectively provided for in the nervous system, as is the more direct translation of impulse into action.

To continue in the pedagogic vein, I add an illustration or two. The following occurrences are about equally frequent: I enter the house at evening,—my mind I know not upon what business of its own,—and am recalled to the *status quo* by the click of the night latch which I have set wholly without intending to do so, for this evening it is to be kept free for a late arrival. My habits have taken it upon themselves to attend to this bit of business through suggestion of hour or occasion, just as they often needlessly wind my watch when I change my waistcoat. Type number three of lapse is presented by the occasion upon which I descend to set the night-latch, and find

I have already done so, doubtless in an absorbed moment, but consciously have no record thereof. The intermediate situation may result in my forgetting to set the latch altogether; so clear was the intention to do so, that the act seems complete without a record of its fulfillment; or again I may be in doubt whether the latch was set or not (though if set, it was intentionally set) and find about equally often that the second mission was a necessary or a useless one. All these several modes of normal lapse have their counterparts in abnormal situations, both being comprehensible in terms of subconscious expansion or usurpation of function.

It is because action consummates the psychic wave that its impairment forms at once the outer index and the inner clue to the difficulty. The most readily formulated situation is the extinction of the guiding initiative. Normally this is possible only for brief periods, for the reason that whatever else I relinquish to subconscious support, I must guide conduct or the movement will cease, at all events cease to go forward or in the desired path. If I yield a little, my mind begins to wander, and my work stops. My subconscious habits will carry me only over this and that familiar gap, once I am well under way. But to work, I must keep my energy going, my thoughts active, my expression ready, in order that my writing continue. But abnormally there occurs what is known as automatic writing. While the hand writes, a fair measure of orientation may be maintained. The subject may talk with you and yet continue writing; or it may be that he is but partially accessible to sensory appeal. He has the feeling that some extraneous force is guiding the pen, that the thoughts are not of his furnishing, the composition not his creation. This abeyance of the feeling of initiative leads to various assumptions. It presents itself as the feeling of inspiration, the attitude of dictation to the words of the muse or of a spirit, or in the religious moods, of God himself. It is very strikingly present in the anæsthesia of ether, and has been termed the anæsthetic revelation. The patient has the feeling that all mystery stands revealed to a liberated insight. To Sir William Ramsay it came thus: "An

overwhelming impression fixed itself upon me that the state in which I then was was reality; that now I had reached the true secret of the universe in understanding the secret of my own mind." To Mr. J. A. Symonds in these words: "My whole consciousness seemed brought on to one point of absolute conviction; the independence of my mind from my body was proved by the phenomena of this acute sensibility to spiritual facts, this utter deadness of the senses." To Professor James still more explicitly: "Truth lies open to the view in depth beneath depth of almost blinding evidence. The mind sees all the relations of being with an apparent subtlety and instantaneity to which the normal consciousness offers no parallel." To Dr. Holmes likewise: "The veil of eternity was lifted. The one great truth, that which underlies all human experience and is the key to all the mysteries that philosophy has sought in vain to solve, flashed upon me in a sudden revelation. . . . As my natural condition returned, I remembered my resolution, and staggering to my desk I wrote in ill-shaped, straggling characters, the all-embracing truth still glimmering in my consciousness. The words were these (children may smile; the wise will ponder): 'A strong smell of turpentine prevails throughout.'" Doubtless the incongruity between the impression and the reality is no greater in the last instance than in the others; and as Dr. Holmes bids us ponder, let us note that the fact recorded indicates some measure of orientation to the forsaken world of sensory experience—an instructive factor in other records—and again, that the very absence of obstruction, of thwart, or hindrance, induces the feeling of revelation, suggests in fact in the philosophically disposed, abeyance of mental effort, the dissipation of initiative. In the less deep invasions of the self-feelings, it is easier to trace allegiance to the experiences of the normal self; and the source of the knowledge revealed in most automatic writing is quite plainly that of the waking self. Here all depends upon the depth of the fissure that has arisen and the degree of purposive activity that may be maintained, while yet incorporation, orientation and initiative are handicapped. For such a state the word "dissociation" is peculiarly apt,—a term that will find explication as we proceed.

One may summarize at this stage that a typical result of impairment of initiative is impulsion. The subject is impelled in hypnosis or again in the intrusions of hysteria (all of which in turn have an analogy of status though possibly not of origin with the irresponsible impulses of pronounced insanity) to carry out an action, even though so much of his normal character as remains, struggles against it as needless, irrational, wrong, or unseemly. Such an individual retains an awareness that the act is going on, that it is his act, and that accordingly he may or must invent some show of reason to make it seem plausible. In brief, so long as he is in the hypnotic condition that condition accepts the act as its own, for in that phase of consciousness the act arouses a feeling of initiative. Upon awakening his alert fully privileged consciousness, that takes up the trail where it was relinquished to the handicapped self, and may know nothing of the other action whatever. We conclude that so long as we find actions going on within us with a feeling of initiative we acknowledge them as our own, being ignorant that the act has been imposed by an extraneous suggestion. Such is the state of hypnosis directly, such is indirectly the state of natural somnambulism, and such with subtle and puzzling variations is the hysterical state. In contrast with these stands the trance states, the intoxication of drugs, the lighter stages of anæsthesia. Here the feeling of initiative slips away through loss of the sense of effort, and what the subject finds expressed by or through his organism he attributes to some external agency. Yet both are instances of handicapped or distorted initiative.

Anæsthesia, hallucination and impulsion thus become the more typical issues of handicapped privileges of a rounded psychic movement; and it is pertinent to inquire what it is that prevents the appearance of these mental distortions in the normal state. Preparatory thereto may we also ask, what then is the normal state?

It is perhaps intelligible why we have no special term, more distinctive, for this routine being, just mentally alive. We feebly call it the waking state, opposing it properly enough to

dreaming, yet realizing how inadequately this describes it. I came upon a friend the other day standing at the door of his house and asked him what he was doing. He replied, "Waiting for the postman." What an incongruous description for an occupation. What he really was busy with mentally, to feed his mind while waiting, may have been some philological speculation (for such is his calling) or watching aimlessly the ice-boats scurrying across the lake, or reflecting upon his sins, or his debts, or engagements. The sudden and magnanimous offer of "A penny for your thoughts" takes many of us unawares; but we rarely catch the stream whose current we are asked to tell. Well! that is the normal and yet most fluctuating state from which we measure departures. And what is most distinctive about it is just this assertive, taking-in-charge, personally-conducted, bossing-the-job attitude which I have asked you to call initiative. Accordingly if you tell me that there is a lion in the room, or that the fountain pen is a stiletto, I laugh at you. My mental alertness tells me otherwise. You cannot arouse an hallucination, because my critical faculties are awake to the actual and reject all that does not square with it as unreal. Similarly you cannot create, nor can there spontaneously arise, any large areas of mental anæsthesia. The very implication of this normal wakefulness is that I am awake to a comprehensive range of appeal. You may pick my pocket when I am falling into a doze, or when I am absorbed in the shop windows—for the loss of orientation on the one hand, and the narrow concentration on the other, contract my incorporation. But you would have to be very expert in your craft to ply your trade while I am particularly and objectively alert.

Similarly in regard to impulsion. I may find myself momentarily beset by an irrational impulse; but it does not reach my muscles because I check it, or my ingrained habits check it for me. And so again if you wish to train me in automatic writing and ask me to let my hand rest and care no more about it, I cannot comply. The hand is too much mine; I cannot disown it; and I cannot do it, because I am normal, because my incorporation and initiative include all that happens to the

hand. The automatic writer has the knack of the nervous system that permits him to do what I cannot. Supposing, once more, that an impulse arises in me, I may state again that the reason why it does not reach expression is that all the avenues of expression are already absorbed and taken possession of by the expression of my voluntary conduct. We have only one muscular system; and that has been made available—every organized bit of it—to the expressions of the normal consciousness. In this fact lies the essence of a unitary, consistent developed self. So it results that when this hypothetical impulse arises, it must do one of two things; it must oust the pilot or drug him or in some way incapacitate him, and get possesssion of the whole mechanism and use so much of it for the expression of its purposes as it requires; or it must disengage a part of the motor mechanism of expression and utilize that without arousing the suspicion of the theft. The last is the ordinary status of automatic writing; the former takes place in hypnosis, and more interestingly in alternations of personality and similar dissociations.

At some stage of my presentation a brief digression is necessary to enable me to pick up some loose threads and weave them into the main strand of my discourse. I might have emphasized at each stage of my story that the most distinctive factor of abnormality is temperament. We all have experienced the lapses of absent-mindedness; but the extreme instances occur in those by temperament distrait, disposed thereto by some inner, natural trick of their brain functioning. The tendency to enter the hypnotic state is similarly conditioned. Hysteria is but an exaggeration of temperament. The ability to enter the trance state, to write automatically, are all similarly significant. The student of mental abnormality cannot create his material but must study it as he finds it; and he comes to know where to suspect its presence by becoming keen in the detection of other revelations of temperament. He does this at least in so far as he develops a clinical aptitude in his chosen career. Let us note then that as we transfer attention to the more abnormal and unusual aspects of dissociated conduct, of handicapped

mental procedure, we are entering the field within which temperament is dominant. It is no longer possible to describe types but only individual cases.

I likewise have been waiting for an opportunity to insist that a phase of our personality as vital as any, stands in contrast to what I have been in the main describing, while yet it co-operates with it; to indicate that much of the mental procedure is not thought or action but feeling; that to understand mental normality and abnormality alike, we must enter intimately and sympathetically into the world of the emotions. These motivate conduct, stimulate and supply the thought-progression, permeate every avenue of the mind's approach, and cluster with peculiar tenacity about the central, personal self, with all its liability to barometric changes of esteem and disparagement. Every phase of our exposition could have been shaped to embody an emotional or an emotionally tinged experience as an intellectual one. Particularly is this aspect of the mental life important for the clue to abnormality and the intrusion of the derivative and supporting aspects of mental progress.

With these obligations suggested if not met, I reach the specific goal of my essay, the formulation of subconscious functioning in its abnormal embodiment. Believing as I do in the illuminating power of clinical experience I must dwell yet a while longer in the descriptive field. The realm to be entered is an attractive one, that of handicapped, altered, distorted and divided personality. Concordantly with our previous analyses, such lapse will reveal itself in the mode of behavior of the incorporative, orientating and initiative privileges. The curtailment will be more comprehensive, more variable, more pervasive. Equally will it vary in depth as well as in breadth and contour; and yet again in one further aspect very important to the clinical comprehension, the mode of onset or origin. I shall begin with the matter of depth. The lighter invasions of the personal integrity will be in the nature of the semi-objective projection of romancing, forfeiting some privileges of orientation but maintaining the scene of the invasion free from encroachment upon the practical life, the every-day vicissitudes

of conduct. It is these that blossom profusely under the emotional incentive of adolescent perturbation. It is not accidental that cases of wayward personality occur typically in young women of unstable, possibly hysterical temperament, as abnormalities of the maturing of the adult self. The abnormal culture then finds a favorable soil for its nurture. The dramatic romancing of this period gives it encouragement, and like much else, it grows by what it feeds upon.

I cite, because of its accessibility, a case not difficult to parallel in less developed form—that of Mlle. Hélène Smith. This young woman of bourgeois origin and amid commonplace surroundings was given to day-dreaming, the theme ever centring about the unusualness of her own personality and its probable destiny. Her real self—not the one that served as clerk in a shop at Geneva—she regarded as endowed with peculiar sensibilities, and in subconscious reservation elaborated for this *alter ego* a somewhat systematic idealization. The passive indulgence—which under the stress of a practical busy life might well have dropped its petals and blossomed unseen—was revived into artificial expansion by the discovery within herself of the power of automatic writing, and by the significance attached to her utterances by her spiritualistic-minded friends. Thus encouraged, she began to give séances after the manner of converts to this modern form of an ancient belief, and to develop in her trances a series of dramas with successive change of rôle.

I must confine myself to the most bizarre of the three dramatic sequences that constituted her trilogy. The scene secures freedom from the impertinent restrictions of reality, by being laid upon Mars; and in turn the stage setting is elaborated, being provided with a flora and fauna exotic and distorted somewhat after the manner of Lear's nonsense botany, with a recognizable blend of the oriental. It is all juvenile in conception and is in its detail quite insignificant. More significant is the development under the same set of motives of a Martian language, quite consistently carried out, and in fulness of time yielding a characteristic alphabet, a simple syntax,

and a creditable vocabulary. The messages thus revealed are in the nature of fulfillment of suggestions implanted by intent or by implication by her interested clientèle, and when not thus specifically occupied embroider a tale in which the leading lady—alias Mlle. Smith—finds a stage and an audience for what was previously composed in the underground workshop of her ruminations. From an intellectual point of view the most substantial achievement is this invention and retention of an artificial jargon with its strange alphabetical symbolism; and characteristically let it be noted that it was just this feat that required longest incubation and presented itself in successive steps; first a few sporadic utterances in the unknown tongue, then a gradual accumulation of vocabulary, with a few simple syntactical complications; lastly a few words in strange character, and even at the end never fluently written, always clearly suggestive of a slow and careful ripening. For the other dramatic episodes—the one Persian in setting and of mediæval character, and the other bringing forward the rôle of Marie Antoinette—I must refer to the protocol, calling attention only to the fact that these feminine fancies provide a more personal and engaging part for the leading lady.

What interests us notably is in the first place how all these revelations writ in the sympathetic ink of a luxuriant fancy reached decipherment; and again what is the relation of the output to the work-a-day self of Mlle. Smith. Fortunately and characteristically this sleight-of-mind brings its own transmuting formula with it. For the utterances and writings and promptings objectified with a weakened sense of initiative, an alien personality is held responsible. This in the unwarranted and yet not inapt phrase of the spiritualists is called a control. Airy figments are satisfactory to no one; and abstract conceptions to psychologists alone; the local habitation and the name is indispensable as a lay figure at the slightest, as a complex, if fictitious, personality at the best, upon which the embroidered products of the mental loom may be draped and combined to artistic effect. This guardian of Mlle. Smith's inner life is called "Leopold." He guides her hand, interprets the mes-

sages—first by a simple "yes" or "no," later by writing and inspired utterance. Leopold is a somewhat shady character (who with equal propriety might have been called by his intimate friends "candle ends," by his enemies "toasted cheese") and is psychologically the measure of overlapping of the directive and the subconsciously elaborated self, who alone—in one stage at least—possesses and manipulates Mlle. Smith's organs of motor expression, and unfolds the secret of her mental incubation. Now, objectively we are not surprised to learn that the language spoken on Mars, while uncouth in sound, has a notably French syntax, French being the only language that the subconscious and the conscious linguist in this case knows; that some of the incidents woven into the *mise-en-scène* are of bookish origin, others transformations of pictorial suggestion, and the stray impressions of a sensitive observation; while still others—as is natural—defy the attempt to trace them to some assignable provenance. Finally and most essentially are we interested to know how *real* is the invasion of this trance production; how intimately she *is* rather than *acts* the rôle of her trance personalities. The evidence is quite clear. The invasion is for the most part light. The shop clerk is but very rarely and only in the most mature stages of the evolution troubled by any hallucinations, or anæsthesias or impulsions. Once she sees Leopold's face or a Martian picture, or has a presentiment which causes her on the streets of Geneva to choose a circuitous path to her home, or to remember by subconscious impression some detail of her business. As you see, Leopold and the rest of her subconscious troop know their places and do not emerge from the stage entrance and appear in masquerade upon the highways of her practical life. And likewise within the trance she retains some incorporative and orientative power. When as Marie Antoinette she smokes a cigarette and the bystanders comment upon the historical incongruity, the offense is never repeated, though the banquet of which Marie Antoinette partakes in robust appetite makes no impression of satiety upon Mlle. Smith when she awakens to the sight of a scattered feast, and though, again, her comrades of the banquet are no longer

for her plain citizens of Geneva but lords and ladies of the French court. Thus the interpretation, however fragmentary, is really consistent; and the incidents when stripped of their adventitious detail reveal a plot which the psychologist may with some satisfaction set forth.

I must pass at once, and I fear with still more ruthless curtailment, to the complementary type of drastically real invasion of a wayward personality of similar adolescent origin, but grafted upon a far more abnormal and hysterical temperament: I refer to the well known case of Miss Beauchamp, so graphically biographied by Dr. Prince. Displaying the usual impressionable day-dreaming indulgences of adolescence strongly tinged with the emotional personal centring, to her the world in which she lived was almost little more than a filmy screen against which the transposed figments of fertile fancy were realistically projected. Yet combined with this there was exercised a rigid control of these complex impulses, sufficient to conceal from her friends the troubled nature of her mental intrusions. Thus, a college student at the age of twenty-three, nervous and erratic but in good standing and well liked by her friends, she came under professional observation, and in Dr. Prince's words pertinent to the period of her greatest personal instability: "She may change her personality from time to time, often from hour to hour, and with each change her character becomes transformed and her memories altered. In addition to the Real, Original, or Normal Self, . . . she may be any one of three different persons. I say three different persons because, although making use of the same body, each, nevertheless, has a distinctly different character; a difference manifested by different trains of thoughts, by different views, beliefs, ideals, and temperaments, and by different acquisitions, tastes, habits, experiences, and memories. . . . Two of these personalities have no knowledge of each other or of the third, excepting such information as may be obtained by inference or second hand, so that in the memory of each of these two there are blanks which correspond to the time when the others are in the flesh. Of a sudden one or the other awakes to find

herself, she knows not where, and ignorant of what she has said or done the moment before. Only one of the three has a knowledge of the lives of the others, and this one presents such a bizarre character, . . . that the transformation from one of the other personalities to herself is one of the most striking and dramatic features of the case.''

In this troublesome tale we have the deepest invasion of the self's integrity; and hallucinations, anæsthesias, and impulsions beset the rounds of daily life and rob it of all possibility of peace or consistent maturing. The endless strife, compromise, victory and despair, strategy and counter-strategy of this tragic conflict I cannot stop to recount, nor can I suggest the therapeutic measures used with endless patience and discernment to bring about a gradual dominance of the normal personality and the restoration to a fair degree of mental health. I must confine my interpretation to incidents that illuminate the relations of the struggling selves in terms of our accepted analyses. This brings upon the scene one ''Sally,'' who in the drama which Dr. Prince was tempted to entitle ''The Saint, the Woman, and the Devil'' may be said to be the incarnation of the party of the third part.

Sally's disposition and the delight she took in tormenting her other self will be sufficiently evident in an incident or two: ''Miss B., who had an abhorrence of insects and reptiles, found a box neatly wrapped, from which, as she opened it, six spiders ran out. Sally, who claimed to be subconsciously present to witness the effect of her practical joke, thus describes the incident: 'She screamed when she opened the box, and they ran out all over the room.' Sally, who felt no pain or fatigue, would walk to a suburban town where she would wake herself up as Miss B., 'who, utterly stranded and without money in her pocket, was obliged to make the journey back on foot, arriving utterly exhausted.' Or again Sally would entangle the worsted yarn of the fancy work that engaged Miss B.'s leisure, wind the threads from picture to chair and around her person, finally hiding the ends in the bed. 'Then Sally, standing in the midst of this perfect tangle of yarn, wakened Miss Beauchamp, who came to herself in the maze.' ''

With such a preamble, one is not astonished to learn that when Miss B. was preparing to go to Europe, Sally should actually assume the character of her double and only by chance was she frustrated from sending off upon the foreign tour not Miss B. but her counterfeit—all this of course at a later and more nearly convalescent stage of the case. Nor must I wholly omit the true complexity of this situation by failing at least to cite the fact that even the Miss B., the college student who presented herself for treatment, was not the whole or, if you will, not the core of Miss B., the normal personality inherent in the individual towards which, we may assume, a Miss B. of more fortunate temperament would have tended. There is then a third state and in some sense a variant of that; and this fourth variant state proved to be a clearing house through which the obligations of the militant or rival operations could be discharged, the one declared insolvent, and the receivership arranged and authorized for the new unified and reorganized firm. What I have most in view is to utilize this complex situation to illustrate further and in richer coloration the subconscious relationships and vagaries. To bring forward the most salient instance first, let me show that what Miss B. does in a moment of abstraction in the subconscious range of her activity is just that of which the subconsciously dominant phase of her being—in this case Sally—is cognizant. Accordingly when Sally appears she can exercise this peculiar power and relate an incident like this: "She yesterday received a letter from a photographer. She had it in her hand while walking down Washington Street, and then put it in her pocket (side pocket of coat) where she kept her watch and money (banknotes). As She walked along, She took out the money and tore it to pieces, thinking it was the letter from the photographer. She threw the money into the street as she said to herself 'I wish they would not write on this bond paper.'" Possibly the last detail is an explanatory concession from the then dominant personality to its rival, to prevent the latter from breaking through and securing an awareness of the disaster. Still further corroborative is the fact that Miss B. (without losing

that phase of her identity) may be thrown into a trance-like condition in which she sees as if reflected in a shining surface, some of the incidents dominated by the "Sally" personality; and in such a vision she actually saw herself walking down the street tearing up green pieces of paper and putting the letter into her pocket.

Still more remarkable and equally corroborative of the status here assigned to these actions is an instance of anæsthesia, peculiar because with both phases of consciousness available as witnesses we obtain an illumination of the shield from both the golden and the silver side. While fingering a chain upon which some rings were strung the chain parted, resulting in the loss of some of the rings. The other Miss B. became convinced that all the rings were lost, and "Sally" tried to persuade her otherwise. "I have put them on her finger," says Sally, "but she won't see them, Dr. Prince; and I have taken her hand and made her take hold of the rings, but she won't feel them." Similarly when Dr. Prince awakened her in the other personality, he could click the two rings together, or pull her head by the chain to which the rings were attached about her neck, without breaking through the anæsthesia. The possibility of one phase of consciousness thus corroborating the anæsthesia of the other suggests an advanced phase of the dissociation, and may in itself be suggestive of a *rapprochement* of the two activities.[1]

These incidents must suffice to illustrate how difficult may become the intercourse of a divided personality, and yet that such complexity is but the issue of the same order of dissociation which in its simpler formulæ yields concrete and intelligible values. What is most startling is that out of such disorder

[1] It is well in dismissing this case to record that it is extremely difficult to avoid in such dissociations the creation of an artificial or suggested relation and, again, the provoking of the very phenomena that are regarded as spontaneous. While such a product approaches simulation and deception, such terms require considerable toning to adapt their usual implications to the abnormal status. The ultimate criterion is the confidence in the discernment of the professional student of the case.

rival personalities and not merely interruptions of normal states should result. We do not speak of our dream selves but of our dream states, accepting these gaps and transformations as normal incidents of the mind's vicissitudes. It is obvious that such dream states are sporadic, do not synthetize, do not accumulate experiences connected with the self feelings, and incorporated with a memory sequence, and motivated by desires, and distinctively achieving the control of a motor mechanism for their expression. This truly constitutes the *leitmotif* of these dramas, though another story is built upon the same lines of composition.

An equally pertinent yet distinct set of episodes emerges when we consider not the upbuilding but the dethronement of a self already established; and yet another when we consider mixed cases in which the very disintegration is conditioned upon a natural disposition to aberration of this type. Most worthy of citation in this instance is the case of the Rev. Mr. Hanna, though it must be said at once that cases in this realm are not typical but individual. What alone I shall have time to emphasize is the fact that after a sudden incapacitating fall a bereft personality awoke, ignorant of all the vicissitudes of a varied and mature life, shorn of all possessions even to the recognition of the commonest objects and their uses; that there intervened a period of slow reinstatement of function, in the latter stages reinforced by direct and vigorous stimulation; and that finally the older and mature personality reappeared, at first fitfully and then more stably, until in the end a fusion of the reacquired and the original personalities took place with a consequent restoration to normal health. The peculiar value of this case is that during the periods of alternation of the bereft and the original Mr. Hanna, there came to exist just that relation of dominant to suppressed realm of the mental efficiency that is characteristic of the intercourse of the conscious and the subconscious strata. A demonstration of ideal cogency is that furnished by Mr. Hanna's dreams during the period of reconstruction. These were of two types, the one weak and difficult to recall, the other clear and vivid picture dreams. The latter

were really recollections of the lost life, though in reporting them the new Mr. Hanna naturally did not recognize them as such. In one of these appeared a railway station upon which were painted the letters N-E-W-B-O-S-T-O-N-J-U-N-C-T-I-O-N, a set of letters that to the bereft Mr. Hanna brought no enlightenment, and yet were accurately visualized. In the station was a man who revealed his name, whose costume could be described, and who through Mr. Hanna's later recollections could be identified as an actual acquaintance. Quite similar in status is the fact related by Professor James in his case of Mr. Bourne, who disappeared suddenly and wandered away to a small town, where as Mr. Brown he kept a small shop, and awoke months later to find himself mentally stranded, knowing not where he was, and returning in memory—as though no gap had occurred in his life's sequence—to the day of the first abandonment of his original personality. Now, three years later when Mr. Bourne, normal throughout this period, was hypnotized and the "Brown" personality recalled, he assumed the "Brown" expression of face and manner and recounted details of his life as a shopkeeper which were hidden from his alert consciousness. Just so when really Mr. Brown he had on one occasion arisen in prayer meeting and recited incidents which came from his normal experience as Mr. Bourne. Briefly, then, though these cases of reduced and enfeebled personalities require special interpretation by other formulæ than those which we have been tracing, they reveal decided affiliations to the former group, and reinforce the scope and value of our principles.

I am well aware that personally conducted expeditions have their drawbacks; the passenger has an interest in looking to the right while the undaunted conductor regards the left as more engaging; the one lingers where the other wishes to skip, and rushes by where for the other interest holds on. Let me then justify the perspective of my discourse and in so doing venture your further disquietude by pointing the moral which the tale adorns. I have insisted that the status and conception of subconscious functioning must be derived from a somewhat intimate appreciation of the mode of its participation in the

normal economy of the mind. On the one hand stands subconscious impressionism, the simple fact that we are and have become diffusely sensitive to our environment and that the oscillations of our mental searchlight are regulated on the whole by consistent though versatile interests. There is, next, subconscious facilitation, which expresses the supporting procedures that are carried on in the underground workshop of thought, the predigestive, supporting stages of preparations which we cannot altogether command and which yet we do not merely passively await. The happy support of the associative mechanism it has been termed, when applied to the process of thinking things over. With particular emphasis have I directed attention to the fact that the mind's operations are of two affiliated yet divergent moods: that of typical wakefulness with an alert availability of the full rounded privileges; the other a falling back upon more passive, natural meandering, which when more completely developed we call revery. I have suggested that there is a seeming rivalry between the two, to which the advice of "Work while you work and play while you play" seems to appeal; and yet that the deeper draughts upon the imaginative concerns and the closer affiliation with mood and temperament which the latter entails is as significant as any other phase of personality. For this reason we take some measure of a man as readily from his play as from his work, and possibly even from his cups. Pursuing this distinction a stage or two farther, we realize that it is the directing, thought-controlling, goal-set activity upon which all training is concentrated, and the successful functioning of which constitutes normal mental health. It is as important, however, to let go as to hold on; and in the trials of insomnia, in the tensions of fatigue, in the restlessness and hesitations of nervousness, we see the type of disturbance that undermines by not giving abeyance and subconscious quiescence their due. At this stage and at my own peril, I detained you by some analyses of just what the normal mental progress entails, what is implied in the very normality both of a moment's procedure and of the integrated personality that results from the accumulation and

maturing of our complex selves. Taking advantage of the data thus assembled, I reminded you that the resulting issue is after all but a compromise of rival personalities; that the normality and the unity of the self is an achievement that stands forth upon the supporting acceptance and rejection of the selves outgrown, the selves suppressed, the selves that yet retain at times an unacknowledged, at times a vacation type of existence.

Having put your attentive indulgence to the test, I from the outset prepared you for the useful and the disturbing aspects of these subconscious supports of our work, our play, and our personality. Consciousness is useful; but the mode of its use is complex and the successful regulation thereof an art. It is this at all events in difficult or unstable temperaments whose maturing involves storm and stress and reaches a safe anchorage after much tossing about on uncertain seas. Yet almost everyone may realize in miniature within his normal experience, the nature of the perplexities which writ large or in strange characters excite our amazement. The lapses of absent-mindedness are peculiarly instructive because of their intimate domestic familiarity and again by reason of their versatility; yet more valuable—as indicating the type of *milieu* that the abnormal demands—is that furnished by dreams, in which we forsake the normal privileges of the waking self and realize how naturally chaos and cosmos meet in a subjective realm. Had we never dreamed, never been absent-minded, never given over to revery, never indulged in half directed day-dreaming, never been subject to wayward impulses, never beset by hesitations, never experienced strange feelings of unreality, of slight gaps in the resumption of our normal selves, we should be cut off from a sympathetic appreciation of what mentally abnormal states are, and how with persistence they may invade the mental domain and make of life such a distortion as the conflicting personalities of Miss B. But fortunately no one is hopelessly sane; and even the most stolid incarnation of the office-stool qualities of the mind must be subject to some occasional holiday fancy that proves his humanity. If, however, one must select the most favorable culture for the exhibition of the traits richly

illustrative of the wayward issues of the subconscious, it is undoubtedly that of the hysterical temperament. Slowly has the psychologist come to realize that the word "hysteria" is one of the most significant in the range of language. The physician is quite as much at fault for this tardy recognition as is the traditional temperament of the scholar which kept him within the cloistered problems of academic interest. It is only recently that the perspective of symptoms that make up the hysterical diathesis has been intelligently set forth. Dominating is a mental and emotional instability, an over-centralized sense of consciousness connected with the emotional appraisal of experiences, an undue giving over to day-dreaming, a lax distinction between reality and figment, a weak hold upon the normal practical objective interests of life. Combine these in mild quality, without serious physiological impairment of nutrition, and you have mere eccentricity, possibly of temporary status; but exaggerate one or the other aspects of the situation, aggravate it by unwise environment or unfortunate accident, particularly in the emotional sphere, or let it chance to find nourishment amid the daily routine, and you may have troublesome instability, malingering or hypochondriac invalidism, evasive and treacherous posing for sympathy and the desire to be interesting; or in another formula, extreme self distrust, false accusation, unbidden thoughts, ill-timed impulses, and all the agonizing tortures of an ingrowing mind. Consciousness truly has its foibles and accidents, its weaknesses and diseases; and it is because of these and their bewildering and kaleidoscopic complexity that the psychologist and physician find a common interest in their decipherment, a common desire to understand and administer to them. It is because I am convinced that the stages of right understanding lead through a survey of the normal behavior and liabilities of consciousness, that I have asked you to follow me upon the trail of the subconscious.

Morals are effective inversely to their length. Yet easy solutions are misleading. The simple life offers no ideal which the psychologist can accept as a beacon or a refuge. The waters upon which he sails are too vast and too deep, the currents too

diverse, the conditions of sea and sky too variable, the seasons too irregular, for any simple rules of navigation. Yet the whole art is based upon the fidelity of the compass, the faith in the illumination of our nature that scientific investigation confers. The demand for practical benefit is insistent, and when fairly presented, legitimate; for, after all, harbors must be reached, the traffic kept going despite our ignorance and the perils of the deep. Within our own day and within our own land have appeared the most comprehensive attempts to regulate human life by an appeal to the mental nature, and specifically by utilization of subconscious influences. Let the physician not be dismayed by the fact that the most widely heralded and popular systems repudiate his status, and place drugless healing and anti-medical ministration as modern consummations side by side with wireless telegraphy and horseless carriages. Nostrums are as inimical to the integrity of his career as are absent treatments; and though appealing to a different clientele, their efficacy is similarly conditioned, their perils an equal menace. It has, however, become a paramount obligation of the medical man to find a place in his theory and practice for the range of influences to which I refer. Mental therapeutics must be legitimized; for the mind is of like issue with the body, and sanity is the health of both. The wise incorporation of mental healing can be entrusted only to the trained wisdom of the medical practitioner. That in this pursuit he will continue undauntedly to lease practice upon scientific precept is the warrant of his authority, and despite temporary fluctuation will maintain his prestige. That in this pursuit he is ready to welcome the aid of other disciples with allied interests and community of purpose, is evidenced by the honor which you have paid to psychology in asking me to address you; that thus re-enforced, the practical and remedial efficiency of subconscious influences may be rendered wisely available to mankind, is the hope with which I conclude.

CHEMICAL PROBLEMS IN HOSPITAL PRACTICE *

OTTO FOLIN, Ph.D.,

BOSTON, MASS.,

Associate Professor of Biologic Chemistry, Harvard Medical School; and Chemist to the McLean Hospital, Waverley, Mass.

I.

THIS subject is not a purely scientific one. I shall have something to say about problems, more specifically about biochemical problems related to medicine; but a discussion of "Chemical Problems in Hospital Practice" necessarily also implies a consideration of the conditions which obtain or which might obtain for biochemical research in hospitals.

The first question asked in connection with any scientific problem naturally is, Is it a practical one? Is it a problem which offers a reasonable prospect of yielding tangible positive or negative results? Clearly, the experience and judgment with which the free and unhampered investigator answers this preliminary question determines, in no small degree, his success in research. In no other branch of experimental science does keen discrimination in this respect meet with greater rewards than in biologic chemistry, and in no other science probably is the lack of this discrimination more frequently encountered.

It is not difficult to find reasons which would seem adequately to account for this condition. Biologic chemistry is full of the most important, fundamental, and alluring problems. Many of these are at the same time important problems of agriculture, bacteriology, pathology, physiology, or medicine; and most of them are easy to see and understand, at least in hazy outlines. The inevitable consequence is that from all these de-

* Lecture delivered February 22, 1908.

partments men of every shade of experience and training have been drifting into biologic chemistry and are working on biochemical problems. But the tools, the methods, which are indispensable alike for an adequate understanding of the details of the problems and for effective work on those details, are integral parts of a science, the main facts and principles of which can be mastered only by years of diligent study. It is a plain fact that without a reasonable proficiency in the use of the tools the workmanship must be poor. Some questions in biologic chemistry can be and, of course, are being settled by the help of comparatively simple technic and by men of very limited chemical knowledge and experience. But the larger problems, the systematic working of the important fields of biochemical research, call, almost without exception, for all the ingenuity, resourcefulness, and critical judgment of the trained chemist.

Biologic chemistry is now in practice a recognized independent branch of experimental science. It is pre-eminently a field for research, pre-eminently a field for which a large body of men should be specifically trained; yet it is one into which most of the present workers have drifted by chance after their student years proper were over. There is now in this country an extraordinary demand for proficient physiological chemists, yet only one university has made effective provision for meeting this demand. The universities are still turning out doctors of philosophy in chemistry who also know considerable physics and geology, but none or practically none who are familiar with any branch of biology. And the medical schools are still graduating only physicians. They doubtless believe heartily in the importance of the medical sciences; but they are only just beginning to understand that the development of those sciences demands suitably trained specialists, specialists who cannot grow up in sufficient numbers on the basis of personal initiative alone.

I am not prepared to say that this condition is peculiar to biologic chemistry; it may exist in other sciences as well, and if so may be chiefly a reminder of the fact that it was only yesterday when we had no universities, no schools for the de-

velopment of specialists in any science whatever. The fact that our first physiologic chemist is still in his early fifties certainly indicates that these are pioneer days in biologic chemistry. This may explain but does not alter the fact that we have as yet no machinery for the development of biologic chemists, and therefore have no reason to expect that the demand for such chemists can be met.

It may be thought that this condition, though unfortunate, cannot have much to do with the subject of this paper. It is unfortunate, and, moreover, it has a great deal to do with that subject.

Whether a given scientific problem is practical or not, whether it is workable or not, depends not only on the character of the problem itself, but also on where the work is to be done and who is to do it. It is useless to dream that chemical problems can be solved in hospitals unless the hospitals have men and equipment for work on those problems. Those familiar with the present conditions of supply and demand in biologic chemistry know that men are not now to be had. During the past two or three years almost every biologic chemist in this country has had the opportunity of making a change. And there is no waiting list. The hospitals have, however, cut no appreciable figure in the creation of this condition. At present they have neither men nor equipment for chemical research. They have not even begun to make any effective demand for such work. Notwithstanding the present popularity of biochemical research, notwithstanding the general confession of belief in its importance, it still remains to be seen whether hospital staffs really want it.

Yet the time will surely come when the medical profession will recognize in practice, as it already does in theory, that the large city hospitals should also be centres for biochemical research. The destructive and regenerative processes at all times to be found in large general hospitals constitute one of the most important fields for unceasing biochemical investigation, and into this field should be called the most able men to be found anywhere. Extensive investigations in this region are as im-

portant for the advancement of physiology as for the advancement of pathologic chemistry and medicine; for in disease, as in health, physiologic processes play an important rôle. Indeed, the most direct and important aim of biochemical investigations must be the advancement of our ability to differentiate between the physiologic and the pathologic, and this can be done only when the investigator is as alert for new points or false teachings in the domain of the physiologic as in that of the pathologic.

It is a mistake to think that clinical men in the hospitals can either do or direct such chemical work. They have the most valuable material for biochemical investigations in their possession. Out of the abundance of such material they have made occasionally in the past, and in the future they will occasionally make, observations which can be worked up into distinct contributions to pathologic and physiologic chemistry. But without adequate provision for the thorough sifting and critical investigation of the observations of the clinicians, most of their impressions must remain hopeless mixtures of the correct, the probable, and the impossible. The chemical work on hospital problems must be done by officers on the ground, by men who are in a position to know the available material, and who have the necessary aid of nurses, assistants, and hospital funds; but they must also be men who work on the problems with their hands as well as with their heads. For no matter how well a given piece of work is planned, no matter how clear and plausible the theory of it may appear, the investigator needs to be critical, skeptical, and alert at every stage of the work.

The finest discoveries, the most valuable hints obtainable from a given investigation, are often enough of the most unexpected kind, and often come at the most unforeseen times to him who is really steeped in the work. But steeped in the work a supervisor never is, least of all a clinical supervisor, and rarely is the man who works at a supervisor's problems.

No supervisors or directors are needed for the work. Independence is a necessary prerequisite for originality in research, and the lack of it in so many American laboratories outside of

the universities must, in part, be held responsible for much poor research and for the continuous employment in research positions of men who never have done and who never can do independent work. Not only does the successful research chemist not need a director; he should not be called on to become one. Provide a well-equippd hospital laboratory, even, if necessary, a small one, some current literature, and one or two assistants. Then give the worker the freedom which he should have earned in order to get the position, and the maximum service for the advancement of biologic chemistry will be easily and readily obtained.

II.

Given these ideal conditions for work, what are the problems which the hospital chemist might be expected to take up?

This is a fair question, yet it is a question which no one man should try to answer in full. There should be no difference of opinion on this point, for when a really practical problem is once clearly and correctly formulated, a most important step toward its solution has already been taken. Each chemist will have his own problems and would be likely to use those problems as a starting point at least; and no one, certainly no one else, can foretell where they would lead or where they would connect with the problems of the clinicians.

I shall confine myself to the field of metabolism. So far as I can see there is no more urgent, no more promising line of investigation on hospital material at the present time.

The problems of metabolism have so frequently been the subject of popular lectures that I can hope to tell you little that is new or that you have not heard before. Still, every worker in the field has his own point of view and his own ideas of the relative importance of the different problems and of how they should be attacked.

The dominant idea in the field of metabolism for more than a generation past may be characterized by two words—nitrogen equilibrium. The conception of nitrogen equilibrium has been the illuminating centre from which practically all the metabo-

lism work of the past has originated and to which it has almost invariably returned. It is not to be denied that much excellent work has been done under the inspiration of this conception. I would not minimize the importance of the principle, nor count as useless the premature and, as we now know, unsuccessful efforts of the past thirty years to make it the guide and foundation of dietetics; nor do I fail to see that valuable work is still to be done on the basis of this principle. Nevertheless, it is my belief that in the metabolism work of the future we will do well to step out, in a measure at least, from under the influence of the principle of nitrogen equilibrium.

It is no longer to be questioned that protein metabolism in the animal body can be subdivided into tissue metabolism and the metabolism of inert food protein. This dual conception of protein metabolism is, in my opinion, no less important than the principle of nitrogen equilibrium, nor is the essence of it altogether new. From the experimental standpoint, these two conceptions have, however, been mutually exclusive, and so long as all the competent investigators persisted in making nitrogen equilibrium experiments they could learn nothing of the tissue metabolism. The metabolism studies of the past have been essentially studies of the catabolism of the food protein. The metabolism work of the immediate future, as I see it, should first and foremost be directed toward a study of the catabolic processes which are less dependent on the daily supply of food protein.

Whatever our attitude may be toward the question as to what constitutes the necessary or the most advantageous consumption of protein for different classes of normal persons, the one fact which, to my mind, stands out clear and full of promise is that for limited periods, for periods as long as those of many acute diseases, and for experimental purposes, the question of nitrogen equilibrium can safely be left out of consideration. This one fact has done away with the necessity for indiscriminately stuffing patients with the precursors of urea and uric acid. It has opened the way for greatly enlarged possibilities of feeding the sick for therapeutic purposes, and it

should remove the deadening influence which the monotonous condition of nitrogen equilibrium has for a long time exerted on experimental metabolism investigation.

The metabolism work which is now called for must largely be done on hospital patients. Every class of clinical material to be found in general hospitals must be searched thoroughly and standardized as to its tissue metabolism, and without regard to the chemical records of the past; for those records represent a different point of view, and they were obtained under unsuitable conditions and by means of inadequate analytical methods. It is not necessary, I think, to be an unreasoning enthusiast or to entertain illusions in order to believe in this work. Some of it, a great deal of it perhaps, may yield nothing of direct value to clinicians; but that which has no value to them is exactly the material which can be used from the physiologic standpoint. This line of work is still in its infancy; and from the standpoint of physiologic chemistry, as well as from that of pathologic chemistry, we need large numbers of exact and detailed metabolism experiments, performed expressly for the purpose of throwing light on tissue metabolism.

I venture to predict that we shall learn more concerning the abnormal or subnormal metabolism of the sick on the basis of creatinin and creatin determinations alone than could be learned in another thirty years by means of the nitrogen determinations of the past. Exact quantitative work is, however, the only kind that is not worse than useless. It is only a waste of time to work on any patient from whom exact twenty-four-hour quantities of urine cannot be obtained. The height, weight, muscular development, even the sex of the person, is of importance in the study of tissue metabolism. The diet may be anything that may seem desirable, except meat products, provided that sufficient control experiments are made. The ideal diets for experimental purposes are, however, those which contain sufficient fuel value and minimum quantities of nitrogen.

While this line of work now seems as definite and clear cut as it is promising, it would, in my judgment, be an error to

plan anything grand or "American" for its execution. The factory plan, almost always out of place in research, is certainly out of place here. We have only made a beginning in the study of tissue metabolism, and to get the real value out of the work we must avoid the routine and the mechanical, and must constantly be on the alert for the errors or the unknown gaps in the present conception of tissue metabolism. We do not yet know to what extent urea, uric acid, the so-called neutral sulphur, and undetermined nitrogen play a part in this metabolism; and every worker in the field should work leisurely enough and critically enough so that every new point of attack, every new clue to a more complete understanding of the subject, will be utilized to the full extent of its possibilities. We need a large number of independent workers in this field.

Every kind of well-defined clinical material calls for renewed investigation from the standpoint of the dual protein metabolism. It is impossible to tell beforehand where the most important findings will be discovered. It is practically certain, however, that the field of the common acute fevers will yield important results. The enormously accelerated protein catabolism in fever, and the peculiar proportions of the different waste products obtained in the urine from fever patients, makes as valuable material for constructive theoretic work on metabolism as I know of. A beginning has already been made on the investigation of this material. There are now, I think, at least three papers from as many different laboratories in process of preparation on the metabolism of typhoid fever. And from what I know of the results obtained, it seems safe to say that they will call forth many additional ones. This work has, I think, a direct bearing on hospital practice, for it should show why some diets ought to be better than others for this class of patients.

It will probably take years of patient research to learn what we ought to be able to learn from fever urines alone. As yet no one has gone beyond the comparatively simple scheme of analysis which I proposed some years ago, and that scheme is not adequate for fever urines. The neutral sulphur and unde-

termined nitrogen so abundant in these urines should receive far more attention than they have yet received. I suspect that in these fractions are hidden products which do not belong together.

The extensive elimination of creatin in fevers is another problem the solution of which may be of far-reaching importance, both from a medical and from a biochemical standpoint. From a biologic standpoint I believe that creatin and creatinin are fundamentally different products, and I am inclined to regard the appearance of considerable quantities of creatin in the urine as a distinctly pathologic phenomenon. Whether this assumption will in the end turn out to be true or false is immaterial. Important is only the fact that in creatin we have one of the most interesting and best-known substances with which the biologic chemist has to deal, yet we do not now know whether it is primarily a waste product or a food. Yesterday it was a normal waste product, to-day we have no reason for saying so, to-morrow we shall certainly know.

It is conceivable that the investigation of this question may at last furnish what the nitrogen-equilibrium work has failed to give, a theoretic foundation for a practical doctrine of normal protein consumption. If creatin should turn out to be a food we have at once an explanation of the dietetic value of meat extracts, as well as a reason why meat might be regarded as having an especial and peculiar value as a protein food. In the creatin elimination we should then also have an index to the maximum amount of meat products which can be advantageously consumed. We might then reasonably assume that meats are exceedingly important food products, but that the maximum consumption of meat normally should fall short of yielding creatin in the urine. The more other protein material is consumed, the less meat it would take to reach this maximum value. In diseases like fevers, which yield large quantities of creatin in the urine, all meat products should then be excluded.

It is scarcely necessary to add that I advance this point of view only as a tentative working hypothesis and only because I think it will demand the kind of metabolism work which is now urgently needed.

For the next few years the conception of a dual protein catabolism should be and, I think, will be threshed out on the basis of work on fever patients and on normal persons, with the help of an occasional investigation on such suggestive conditions as pregnancy, convalescence, progressive paralysis, gigantism, and dwarfism. This will clear the ground and incidentally should sharpen our wits and our tools for work on the more difficult chronic diseases, such as rheumatism and gout, and the chemically more complicated diseases, such as nephritis, atrophy of the liver, and diabetes.

The specific problems in diabetes loom up so large and important as to be in themselves worth the lifetime of any chemist having exceptional opportunity to work on them. No generally acceptable explanation for the inability of the diabetic organism to utilize sugars has as yet been advanced, and so long as this is the case such a concrete and well-defined problem demands renewed critical or constructive work. The same holds true for the acid-intoxication theory advanced on the basis of so-called diabetic coma. So long as this definite and withal plausible theory cannot command general acceptance, it should be regarded only as a standing challenge for more work by anyone to whom any special opportunity for work on it may happen to come.

Some of the more superficial observations and conclusions included in the accepted teachings concerning diabetes seem to me to be decidedly open to suspicion. The supposedly characteristic fruity odor emanating from the breath of diabetic persons has, I believe, nothing to do with the traces of acetone which the respired air of these patients contains. I have very nearly satisfied myself that that odor, in most cases at least, is due to nothing else than delicate whiffs of the stomach contents.

The peculiar sweetish odor occasionally encountered in diabetic urines, which is also believed to be due to acetone, is entirely different from the so-called acetone breath. As yet, I have not the slightest idea what this odor is due to, but in this case I am positive that acetone has nothing whatever to do with it.

The qualitative chemical tests for acetone in urine as usually carried out may likewise be regarded as pure fiction, for I have never yet seen a fresh diabetic urine the acetone concentration of which was sufficient to give a positive test with the nitroprusside reaction.

I would not imply that such errors in the teachings on diabetes tend to invalidate the more important teachings based on the sugar, on the ammonia, and on the diacetic and oxybutyric acid. The purpose of this paper is, however, to point out fields for biochemical research in hospitals; and I regard the whole subject of diabetes, and especially the acid-intoxication theory, as a most fruitful field for purely chemical work. I have already on a previous occasion[1] indicated what that theory would seem to call for from the therapeutic standpoint, and I repeat now that the sodium carbonate treatment as practiced must be regarded as a crude and unsuitable application and test of that theory.

It would be going outside the scope of this address to enter on detailed discussions of the numerous relatively isolated problems to be found in the field of metabolism. Small specific problems usually yield the quickest returns and not infrequently good ones. Every chemist knows this and is only too glad to take up the chance observations or suggestions which constitute the starting point for such investigations. Experienced clinicians usually have problems of such a nature to offer. I have endeavored rather to advance a point of view and to indicate broadly the kind of work which it calls for and the kind of material which must be worked up from that point of view.

The goal of the future in the field of metabolism is detailed knowledge of what takes place in the different organs. There are seemingly unlimited possibilities for several generations of work on the specific metabolism of specific organs and its effects on the general metabolism. The final explanations of and remedies for diseases, if they are to be attained at all, will be

---

[1] Jour. Amer. Med. Assn., 1907, xlix, 128.

reached on the basis of such refined metabolism investigations. For the present we need, however, first of all, to learn the more obvious and general laws that govern the animal metabolism. From the standpoint of medicine we must surely first so learn to know the waste products that we shall be able to say with greater certainty than has yet been possible whether a urine is or is not abnormal. This, I believe, can be done on the basis of the tissue metabolism just so soon as the necessary standards for comparison have been worked out.

We need, however, an abundance of reliable statistical material. The normal tissue metabolism from infancy to old age must be standardized carefully by the help of suitable and easily duplicated test diets. I think we shall then find not only that severely sick hospital patients show a deficient or abnormal tissue metabolism, but also that those who are merely weak and debilitated, and who need "building up," will reveal that fact to the chemical test. By those same chemical tests we shall then also know whether a given treatment has produced a general and fundamental improvement or whether it has merely removed some of the symptoms. So far as I now can see, there is no reason why we should not be able to determine with all desired certainty to what extent it is possible to influence the tissue metabolism by drugs, by diets, and by different modes of living. The very stability of the tissue metabolism (as indicated by the constancy of the creatinin elimination) against nearly all fleeting changes of diets and conditions would seem to me to constitute the surest guarantee that this line of work will, at all events, not yield a series of illusions. If well done, it should add a new chapter to the science of metabolism and of medicine.

EMBRYONIC TRANSPLANTATION AND THE DEVELOPMENT OF THE NERVOUS SYSTEM*

ROSS G. HARRISON,
Professor of Comparative Anatomy, Yale University,
New Haven, Conn.

IT is my intention this evening to give you an account of a certain field of anatomical study, with the purpose of showing how the experimental method may be applied to the solution of embryological problems, and more particularly of those that have to do with the development of the nervous system.

It is generally recognized in science that the experimental method, by which we may deliberately vary the conditions bearing upon a natural event, is a vastly more efficient means of analysis than the method of merely observing phenomena as nature presents them to us. The sciences that have used this means of advancement have attained a much higher degree of perfection than those that have not. While, of course, this has been due in a great measure to the fact that the former, the physical sciences, deal with relatively simple phenomena, still it cannot be doubted that those sciences that have to do with living things might have made greater progress had the possibility of experimentation been more fully realized. In physiology this has been done, and with good effect; but until a comparatively recent date it has not been the case with that branch of biology which deals with the form and structure of organisms, morphology or anatomy. In recent years, however, morphologists have begun to experiment, and now this method of study, introduced about twenty-five years ago by Pflueger, Roux, and Born, has found wide application. This is true especially in the field of embryology.

---

* Lecture delivered March 7, 1908.

The complexity of the processes of development and the extreme delicacy and minuteness of the objects to be studied have, of course, tended to limit the field to which the method could be applied. Especially is this the case with the embryos of the higher vertebrates, which are so carefully protected in the maternal body or by complex fetal membranes that they are only to a limited extent amenable to experimentation. We must, therefore, be content with the use of lower forms for this purpose. Yet, fortunately for the possibility of extending our conclusions to many of the phases of human development, we have in the embryos of the frog and the fish forms which are sufficiently closely related to man, and which permit the most varied kinds of experiments.

In general the methods of experimental embryology have been of two kinds. In the one, the whole organism is subjected to changed conditions, as is the case when the medium in which it develops is altered, for instance, by changing its temperature, illumination, or chemical composition. In the second, it is the immediate organic environment of the parts of the egg or embryo that is altered, as when the different substances of the egg are separated by means of the centrifuge, or as when certain parts are removed or others added by transplanting living material from one position to another.

One of the most extraordinary discoveries in the latter mode of procedure was made in the year 1894 by the late Professor Born, of Breslau.[1] While experimenting upon the regeneration of lost parts in the frog embryo, this observer was astonished to find that pieces which had been entirely severed from one another might heal together again. Born then showed that it was possible to heal together parts of embryos in any manner imaginable. All that was necessary was to bring two freshly cut surfaces together and to hold the pieces in position for several hours, when they would be found to be firmly and permanently united. In this way individuals of normal form, but with parts taken from two distinct embryos, could be obtained; also any kind of double monster, or such with a head in place of a tail or a tail in place of a head (Fig. 1). Some

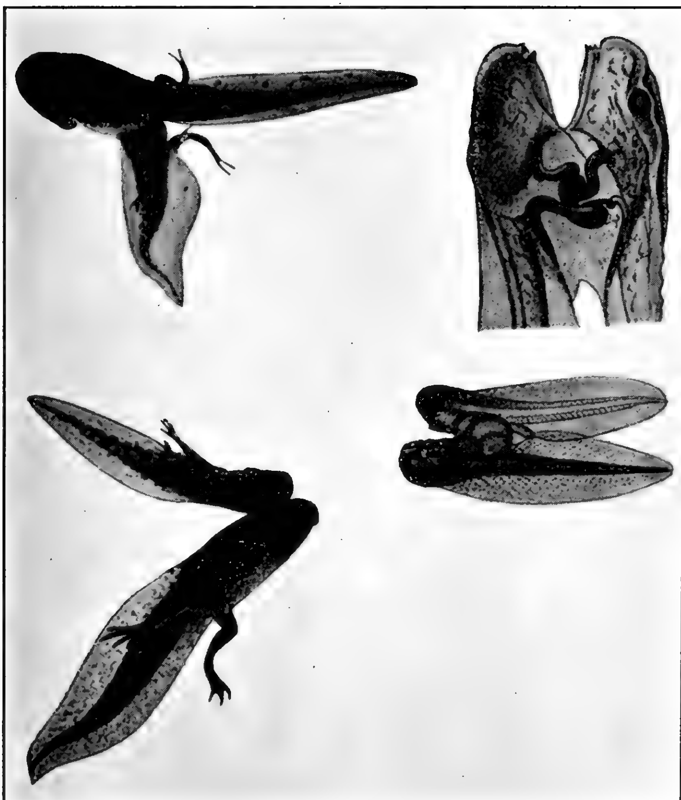


FIG. 1.—Composite tadpoles. (After Born, from Hertwig's Handbuch der Entwickelungsgeschichte).

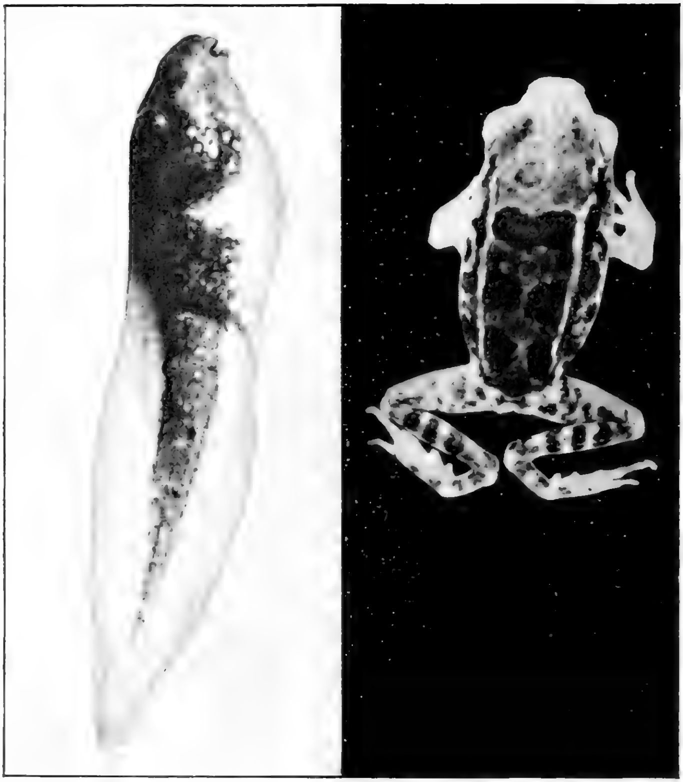


FIG. 2.—Composite individual, as tadpole and as frog. Anterior portion, *Rana pipiens* (*virescens*); posterior portion, *Rana palustris*.

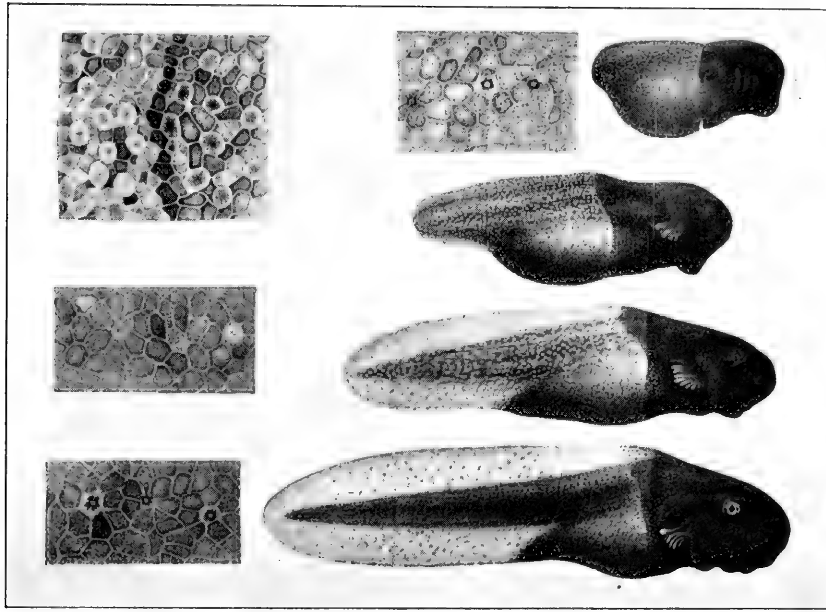


Fig. 3.—Composite embryo: anterior half, *Rana sylvatica*; posterior half, *Rana palustris*. The four figures on the right show the same individual at two hours, one day, two days, and four days, respectively, after grafting together. The figures on the left show the finer surface markings of the epidermis and the sense organs of the lateral line.

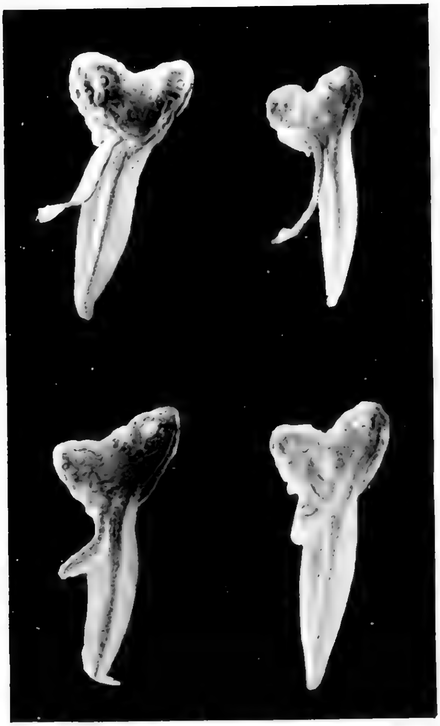


Fig. 4.—Nerveless tadpoles attached to normal individuals which serve as nurses.

of these specimens were reared past their metamorphosis into the young frog. Born showed that even portions of embryos of two distinct species, in fact, organisms as far removed from one another as the common European green frog (*Rana esculenta*) and the fire toad (*Bombinator igneus*) could be united.

These experiments have since been repeated, and amongst my own material I have had many specimens of which the anterior half was of one species and the posterior half of another.[2] Many of these lived for a long time; and one passed through its metamorphosis, becoming a frog of perfectly normal form, showing in each half the characteristics of the proper species (Fig. 2). Obviously an experiment of this sort would be the ideal one to test the influence of the body upon the reproductive cells within it, though unfortunately the difficulty of rearing frogs in confinement from the egg to maturity has, up to the present time, stood in the way of carrying out the experiment to a successful conclusion. Another use to which the union of parts taken from different species may be put is dependent upon the circumstance that the embryos of the several species are characteristically pigmented. For a considerable period in their development these color differences may be seen in each individual cell, and on this account it is possible to follow in composite embryos the wandering and shifting of the parts during that time. I have made use of this method to study the wandering of the epidermis and the development of the sense organs of the lateral line,[3] which may be traced with great nicety in this way (Fig. 3).

These transplantation experiments are rendered possible by a fortunate combination of qualities in the amphibian embryo. As a factor of first importance we find the extraordinary wound-healing power. The healing is very rapid and always *per primam intentionem,* and this to a degree of perfection never obtained in ordinary surgical procedure. Another important factor is that at the time when the transplantations are usually made there is no circulating medium such as blood or lymph present, but each cell of the embryo is capable of maintaining itself independently of its neighbors, living upon

the large quantity of yolk stored within it. On this account it is even possible to make monsters of a great variety of forms, which later, when the yoke is gone, become physiological impossibilities, such as specimens with a tail in place of a head or *vice versa*. As long as food yolk is present such specimens are capable of maintaining themselves in some fashion, and creatures of this character may even be kept alive for a still longer period by a method that I first used to rear tadpoles from which the central nervous system had been extirpated,[4] and which in consequence could not get about in a natural way to obtain food. The method consists in uniting the patient to a normal individual, which serves as a nurse. The vascular and intestinal anastomoses that ensue upon such an operation are sufficient to care for the nutrition of the helpless component, at least for a considerable time (Fig. 4).

In view of the frequency with which the question has been asked how it is possible to perform such delicate and at the same time radical operations, a few words in explanation of the technic will not be out of place. The experiments are usually made upon comparatively young embryos, *i.e.*, from the gastrula stage to those of about 3 mm. in length, with medullary folds just closed. The original method of Born was simple and it was applied to the transplantation of relatively large pieces. The parts to be united were brought into contact along freshly made wound surfaces, were then gently pressed together, and secured in position by placing small pieces of silver wire around them. This is necessary, for, although the embryo at this stage is unable to perform any muscular movements, the action of the cilia which cover its surface is so vigorous as to cause the pieces to separate unless securely held in place. After an hour or two, or even less in favorable cases, the pieces so held will be found to be firmly united and soon afterward all traces of the wound become obliterated.

The refinements of technic introduced by Lewis and by Spemann [5] were made possible by the use of the binocular dissecting microscopes of Zeiss. Under these instruments the frog embryo may be readily magnified to the size of a mouse, and

the long working distance of the lenses allows one to operate with every comfort. With very sharp needles, forceps, and small eye scissors, the points of which are sharpened to the fineness of a needle, or, as Spemann recommends, with instruments made by drawing out glass rods and pieces of cover slips to a great degree of fineness, operations of almost incredible delicacy may be performed. The epidermis of the embryo may be lifted, the Gasserian ganglion may be removed to some other part of the body, the ear vesicle may be taken out and replaced upside down, or the right and left ears may be interchanged, as Streeter [6] and Spemann have done. Small organs or pieces of tissue may be transplanted to little pockets made under the skin or between the larger organs, and they will grow readily in their new surroundings. Again, pieces of epidermis may be taken from one part of the body and be made to cover wounds in other regions. It was by means of such experiments that Lewis [7] was able to show that epidermis from any part of the body could give rise to a crystalline lens when brought into contact with the optic vesicle at the proper stage of development.

Such experiments as have just been described are done without anæsthesia because the embryos in these early stages have neither muscles nor nerves differentiated. For operations in later stages, as in the case of Braus's experiments in transplanting limbs, which were made upon tadpoles already able to swim actively, an anæsthetic is necessary. Chloretone is found to be excellent for this purpose, a solution of from two to three parts to ten thousand of water being sufficient to produce a deep narcosis in a few minutes. The recovery after bringing the animals back into pure water takes place with almost the same rapidity. In none of the experiments are there any complications due to sepsis.

Let us now proceed to consider the application of these methods to the study of the development of the nervous system. The problems here involved which have been the most discussed and which have proved to be the most perplexing have to do largely with the development of the nerve-fibre. We find in

the adult nervous system a most intricate maze of fibres, connecting the various parts of the organism, and in each species of animal the arrangement of these fibres is very constant. How can it possibly come about that these interlacing bundles always connect their proper end stations? What are the factors which influence the laying down of the nerve paths during embryonic development? Before these questions can be satisfactorily answered there are other more concrete ones that must be settled. What is the nerve-fibre in terms of the cell doctrine? Is it an appendage of a cell or does it consist of a multitude of cells? Again, does the connection between the nerve-centre and the end organ exist from the beginning, or is it established gradually as development proceeds by extending out from the nerve-centres? These questions are old ones, and the various answers now given to them had all been given fifty years ago. Each view has had its vicissitudes, but at the present time it cannot be said that any one of them prevails by weight of authority, for each numbers distinguished investigators among its advocates.

We may first take up the question of the constitution of the nerve-fibre. The answer originally given by Schwann,[8] later by Balfour,[9] Dohrn,[10] and many others, and again more recently by Apathy,[11] Bethe,[12] and O. Schultze,[13] is that the nerve-fibre is the product of a chain of cells, which reaches all the way from the centre to the peripheral termination, these cells secreting the fibrillæ within their protoplasm much as an embryonic muscle-cell secretes the contractile fibrillæ. The opposite answer, first stated with perfect clearness by His,[14] and afterwards ably supported by Ramon y Cajal,[15] von Lenhossék,[16] and the neuronists in general, is that the nerve-fibre is the process of a single ganglion cell, and is formed by growing out from the cell towards its peripheral connection.

In reality it is difficult to decide between these two alternatives, as may readily be appreciated when we study, for example, the development of a typical spinal nerve in a vertebrate embryo. At an early stage we find the motor root extending out from the medullary cord, and consisting of delicate fibres,

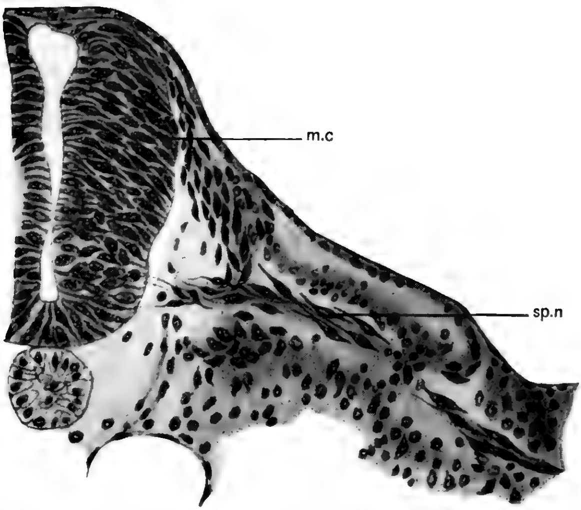


FIG. 5.—Cross-section through a chick embryo of 73 hours to show the beginning of a spinal nerve (*sp.n.*); *m.c.*, medullary cord (after Bethe).

FIG. 6.—Cross-section through the medullary cord of a salmon embryo to show neuroblasts and motor nerve-fibres (*m.n.*) (after His).

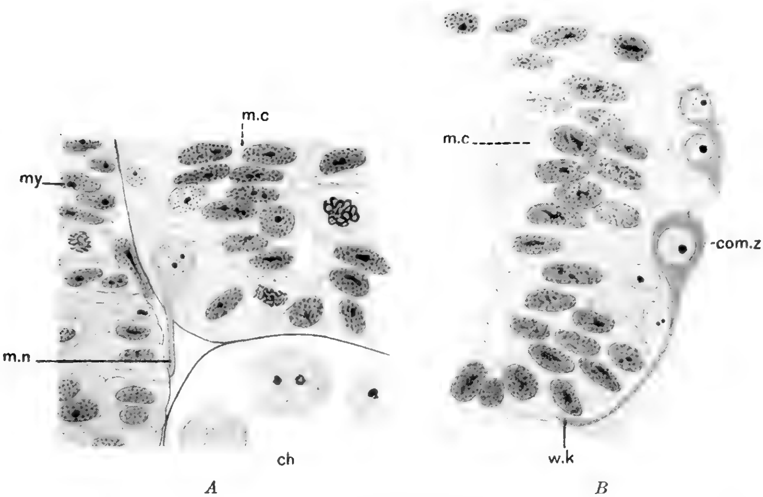


FIG. 7.—Cross-sections showing part of medullary cord of a salmon embryo. *A* shows a motor root (*m.n*) consisting of a single fibre proceeding from a single cell within the cord; *B* shows several neuroblasts and a commissural fibre growing out from one of them, *com.z*.

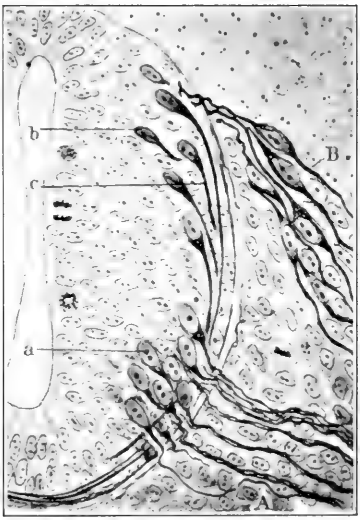


FIG. 8.—Section through the spinal cord of a chick embryo of three days. *A*, motor root; *B*, spinal ganglion; *a*, motor neuroblast; *b*, *c*, commissural neuroblasts. (After Ramon y Cajal.)

with which are intermingled in a most intimate manner numerous spindle-shaped cells. The fibres may be traced into the cord and there may be seen to proceed from certain cells, which are destined to become the motor nuclei of the ventral horn. The question to be decided is: which of these two kinds of cells, the spindle-shaped cells along the nerve, often called cells of Schwann, or the ganglion cells within the cord, is the essential agent in forming the axis-cylinder of the nerve-fibres? The attempt to answer this question, from normal embryos, has been

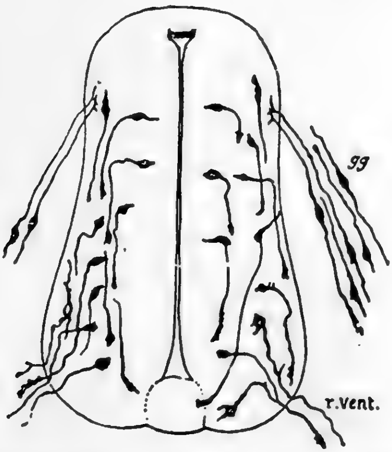


FIG. 8a.—Semi-diagrammatic cross-section through the medullary cord and spinal ganglion of a chick embryo, prepared by the Golgi method. *gg*, spinal ganglion; *r.vent*, ventral root.

largely a matter of individual interpretation, as a glance at the figures will show. Fig. 5, taken from Bethe, expresses one view; Fig. 6, taken from His, and Fig. 7, *A* and *B*, taken from my own study on the salmon embryo, express the other view; and the latter is represented in more diagrammatic form in the familiar Golgi picture, taken from Ramon y Cajal (Fig. 8a). The same is likewise shown in the figure of a section through the chick embryo prepared by the silver reduction method (Fig. 8).

Although my own work upon the normal development of the salmon and frog [17] had led me to a decided opinion in favor

of the cell-outgrowth theory, the attitude of many later investigators showed that we should never be able to obtain evidence from the study of normal development that would convince everyone alike of the truth of either of the views just stated. A decisive answer to the question, it seemed to me, could be obtained only by a more exact method of study, *i.e.*, by the elimination, in turn, of each of the two conflicting elements.

This was accomplished by operations upon the embryo,[18] in which certain parts were removed before the development of the peripheral nerves had begun. The first task, viz., the removal of the source of the spindle-shaped cells of Schwann, which may also be referred to as sheath cells, was complicated by the circumstance that there had been no agreement among embryologists as regards their place of origin. As the weight

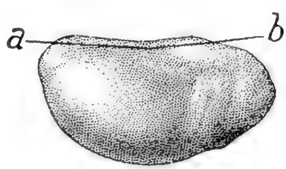


FIG. 9.—Frog embryo 2.7 mm. long. The line *ab* indicates the incision for the removal of the ganglion crest.

of opinion seemed to lean towards the derivation of these elements from the ganglion crest, and as this structure is easily accessible to the knife, the experiments were begun by removing this structure. Embryos of *Rana esculenta* were used for this purpose; and, as it was necessary to begin with a stage in which there was as yet no differentiation of the nerve-cells or fibres, embryos were taken in which the medullary folds had just closed over to form the tube. Such embryos are about 2.7 mm. long. With the aid of the fine scissors, a thin strip was cut off the dorsal surface of the embryo (Fig. 9), removing the dorsal half of the medullary cord, which includes the neural or ganglion crest. The embryo was thus left with its central nervous system as an open groove along the back, the walls of which contained the elements which were to become the motor cells of the spinal cord. In order to reduce to a minimum

the possibility of regenerative processes setting in and vitiating the results, two embryos which had been operated upon in this way were in each case brought together by the wound surfaces and were readily healed together. They grew normally, except for the defects due directly to the operation (Fig. 10), and after an interval of six to eight days they were preserved and either examined in serial sections, or else preparations of the abdominal walls were dissected out and examined *in toto* (Fig. 11). It will be understood that in removing the gan-

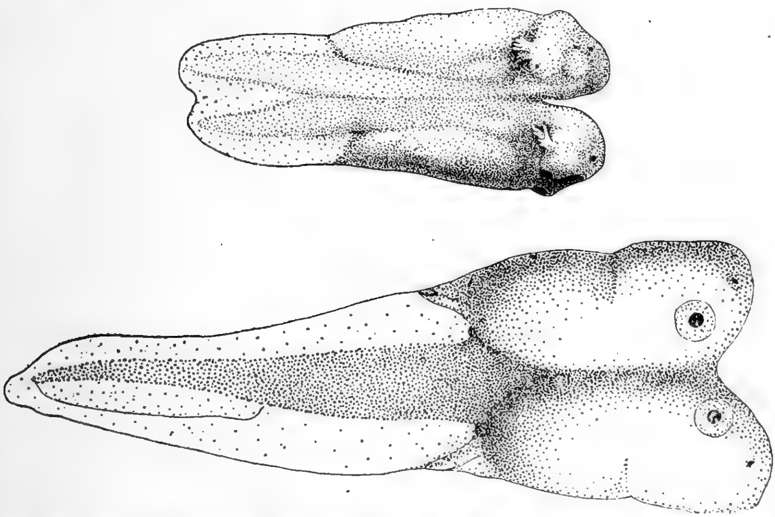


FIG. 10.—Two double embryos, from each of which the ganglion crest has been removed. Upper figure, two days after operation; lower figure, six days after.

glion crest, the source of the spinal ganglia had been eliminated as well as the presumed source of the Schwann cells. The result was that the embryos were found to lack spinal ganglia entirely, as well as sensory nerves, except those derived from the cranial ganglia, which had been left intact in the operation. What interests us most is the character of the motor spinal nerves. These are found to be present, but to differ entirely from the normal condition (compare Fig. 11, *b* and *c*). They are mere naked threads or strands, which extend in nor-

mal position from the spinal cord to the periphery. They may be followed to their extreme terminal points in the abdominal muscle near the ventral midline. In cases in which the opera-

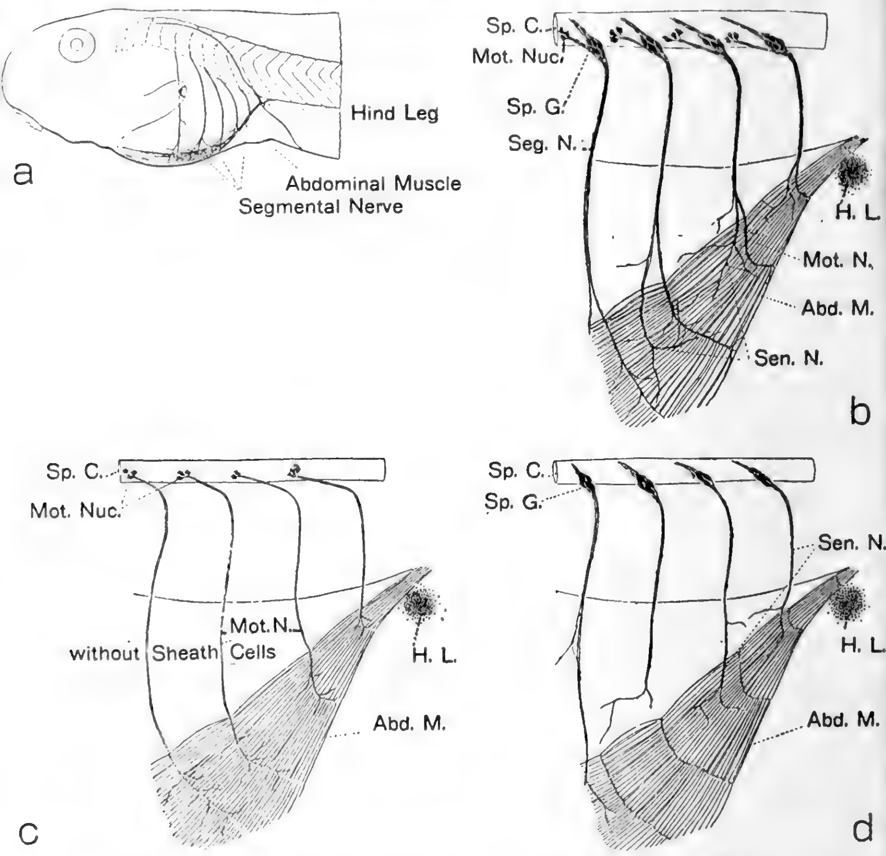


FIG. 11.—Diagrammatic views of the nerves in the abdominal walls of the tadpole. *a*, body of larva showing general arrangement of nerves; *b*, arrangement in normal larva; *c*, arrangement in larva from which ganglion crest had been removed, only the motor nerves showing; *d*, arrangement in larva from which the ventral half of the spinal cord had been removed, showing only sensory nerves. *Abd. M.*, primary abdominal muscles; *H. L.*, hind limb; *Mot. N.*, motor nerve; *Mot. Nuc.*, motor nucleus; *Seg. N.*, segmental nerve; *Sen. N.*, sensory nerve; *Sp. C.*, spinal cord; *Sp. G.*, spinal ganglion.

tion has been exact, not a single Schwann cell can be found in the whole course of the nerves; and in cases in which a few cells are found, sections show that small groups of spinal gan-

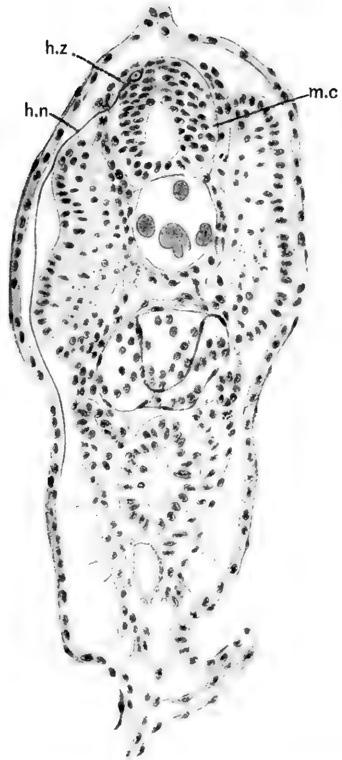


FIG. 12.—Cross-section through salmon embryo showing long nerve (*h.n*) derived from one of the giant cells (*h.z*) in the spinal cord.

glion cells are present, indicating that the ganglion crest has not been entirely removed. The nerves are thin and delicate, and have a fibrillar structure, although it has not yet been possible to test whether they give the specific neurofibrillar reaction with the silver or gold methods.

The experiment shows, first, that the source of the sheath cells, both of the motor and sensory nerves, is in the ganglion crest; and secondly, that these cells are unessential to the formation of the nerve-fibre. The ganglion cells of the ventral part of the medullary cord are capable by themselves of forming the motor nerves. While it has not been possible to corroborate this by experiment upon sensory nerves, owing to the fact that the sheath cells and ganglion cells of these nerves are derived from the same source, still we have evidence, from normal conditions, which bears out in a striking way the correctness of this conclusion. In the case of the nerve-fibres derived from the dorsal giant cells of Rohon-Beard, we have simply naked axis-cylinders (Fig. 12). Likewise in the newt larva the sensory nerves of the tail fin are entirely devoid of cells for a short while during their early development. In other words, nature has here performed an experiment for us, in that she holds back the sheath cells from some nerves until after they have extended out to full length, thus showing that in the formation of these nerves the sheath cells are not an essential element. Another of nature's experiments has been recently recorded by Dohrn,[19] and this corroborates in a very striking way the results above described. In dogfish (*Pristiurus*) embryos it seems that the *n. trochlearis* receives its sheath cells not directly from the neural tube or ganglion crest, but from a particular branch of the trigeminus nerve, the *n. ophthalmicus minor.* In one case which Dohrn describes the latter nerve was inhibited in its development by some unknown cause, and it was found that the trochlearis consisted of naked fibres throughout its entire extent, not a single sheath cell being present from the decussation to the superior oblique muscle.

Having thus established the fact that the ganglion cells

could without the aid of sheath cells give rise to the axis-cylinder of the nerve, it now became of great interest to ascertain if the sheath cells were by themselves capable of giving rise to nerve-fibres when the ganglion cells were excluded. This experiment involved greater technical difficulties than the first, but nevertheless it was found possible to carry it out as follows: The dorsal half of the cord was separated from the rest of the embryo, as in the operation previously described, except that it was left attached at one, usually the anterior, end; then the ventral half of the cord was cut out and the thin strip containing the dorsal half healed back in place. Thus the ganglion cells of the motor nerves were removed, the source of the sheath cells and sensory nerve cells (spinal ganglia) being left intact. The embryos developed normally and remained almost motionless, though after a few days slight reactions to stimuli in the form of quivering movements were observed, and later these were found to be due to incipient regeneration of the motor cells within the spinal cord. Examination of the abdominal walls showed, however, that here only sensory nerves were present (Fig. 11, *d*). The motor nerves were lacking, although in normal individuals they run for a long distance in common with the sensory nerves, an arrangement which would give the Schwann cells of the latter ample opportunity to form the fibres of the motor rami. The fact that none were formed can only be ascribed to the inability of the Schwann cells to form them.

This conclusion has been confirmed by the behavior of nerves that have been deprived of connection with their ganglionic centres after development had begun.[20] In the case of the abdominal nerves of the tadpole, and also of the lateral line nerve, degeneration was found to take place very rapidly after removal of the ganglia, and no signs of constructive developmental changes were ever observed under such conditions. We may conclude, then, that not only do the sheath cells fail to form nerve-fibres, but that they are unable to continue their development or even to maintain the fibres already formed in the absence of connection with the nerve-centre. The opposite

conclusion, which was reached by Brauss[21] and by Branchi[22] upon experimental evidence, may be explained by the fact that these observers did not exclude every possibility of contamination by ingrowth from other nerves; and it is my opinion that this same objection still holds with reference to the evidence for autoregeneration of peripheral nerve-fibres.

Having established the conclusion that the ganglion cells within the nerve-centres alone have the power of forming nerve-fibres, the spindle-shaped cells merely forming the sheaths of the fibres, we may next inquire into the question as to how the nerve-fibre extends from the ganglion cell to its peripheral ending. Is this process a mere differentiation of protoplasmic connections already *in situ*, as Hensen[23] first maintained, or is it an actual outflow of substance from the ganglion cell towards the periphery?

In the past few years the trend of opinion has been unmistakably toward the support of Hensen's theory, according to which protoplasmic bridges are supposed to be left everywhere between dividing cells of the embryo, so that at the time when the nerves begin to differentiate there is already a complex system of protoplasmic connections between various parts of the body; those which function as conduction paths are supposed to differentiate into nerve-fibres, while the rest ultimately disappear. There has ever been something insinuating about this theory, putting, as it does, the whole question of the development of nerve paths upon the physiological basis of functional adaptation; but, brilliant and attractive as it seems, very little real evidence has ever been brought forth to support it. In fact, its mainstay has been the imaginary difficulty of conceiving how the alternative view could be true. "How can it be possible," it has often been asked, "that a nerve-fibre can grow out for a long distance from its ganglion cell and always reach the right place?" However, within the past three or four years a number of investigators, amongst whom may be mentioned Kerr,[24] O. Schultze,[25] Paton,[26] and, in a modified sense, Held,[27] have sought to place Hensen's theory upon the basis of direct observation. But the point to be

decided is really a very difficult one, and one in which the histological method again fails us, refined as the newer neurological procedures may be. It has, on the other hand, been possible to attack the problem experimentally, and with results which seem to me to disprove entirely the theory in question.

It will be readily seen that the two theories differ from one another in attaching to different elements of the embryo chief importance as regards the formation of nerve-fibres. According to the outgrowth theory, the ganglion cell situated within the nerve-centres is the all-important factor; while in the other view it is the extraganglionic protoplasmic structures that play the chief rôle. But, unfortunately for the purpose of devising a clean-cut and crucial experiment, the antithesis between the two views is not complete, for, even according to the first, the organs outside the nervous system are supposed to have some influence in determining the course which a nerve-fibre takes as it grows out, while the second view admits that the ganglion cell has a functional or trophic influence upon the processes of differentiation.

The first experiments of my own having a bearing upon this problem were of a comparatively simple nature, but, though helpful, were not crucial.[28] After it had been shown that no peripheral nerves would develop in an embryo from which the nerve-centres had been removed at an early stage, thus proving that the ganglion cells were at least one essential element, experiments were made in which the immediate organic environment of the developing nerve was radically altered. This can readily be accomplished by cutting out the spinal cord of an embryo before there is any trace of differentiation in the nervous system. After the wound heals there remains between the notochord, muscle plates, and skin a space filled with mesenchyme tissue, which is a portion of the space normally occupied by the spinal cord. Now, if the various fibres which normally arise from the brain and extend as longitudinal funiculi into the cord are formed of protoplasmic processes already situated within the cord, we should expect to find that no development whatever of these elements would take place.

This is, however, not the case, for a few days after the operation very stout bundles of fibres are found extending from the medulla oblongata longitudinally through the mesenchymatic tissue, which has taken the place of the medullary cord. It has been possible to follow such fibres for nine or ten segments, *i.e.,* through the whole length of the trunk region, where they gradually lose themselves in the mesenchyme without showing any definite point of ending. In other words, these fibres have been formed in surroundings entirely different from their natural path and with connections which preclude any possibility of function having played a part in influencing their development. Similarly Lewis [29] has shown that after removal of the embryonic brain the olfactory nerve develops and is found after a few days to extend out from the nasal epithelium and gradually to lose itself in the mesenchyme occupying the position normally taken by the fore-brain. Corresponding results have been obtained in the case of the optic nerve.

The following experiment, which is somewhat more complicated, entirely corroborates the foregoing. The whole trunk region of an early embryo was made sterile as regards peripheral nerves by cutting out the entire spinal cord. Then a bit of the medullary tube, taken from another embryo, was transplanted to a pocket under the skin of the abdominal walls. After the expiration of six or seven days, the abdominal wall was dissected out and mounted *in toto.* The only nerves found in the specimen (aside from the branches of the *r. lateralis vagi,* which come from the head) were those which originated in the transplanted tissue. These were found to radiate in various directions, and not to follow any particular path corresponding to the course of the nerves in normal specimens. It was one of these cases that showed the interesting condition of a nerve crossing the peritoneal cavity. The specimen in question, when dissected out under the binocular microscope, showed an extremely fine thread which extended from the piece of transplanted tissue across the abdominal cavity to the base of the mesentery, where it was attached. It was cut off at this end, and, after the specimen was mounted, the thread was

found to consist of three axis-cylinders, entirely devoid of sheath cells, which proceeded from a group of three ganglion cells, a miniature spinal ganglion, that had apparently been detached from the main mass of transplanted tissue; root-fibres were present connecting this with the main mass. That this nerve had grown where normally no nerve paths ever have been present is clear, although there is some doubt whether it actually did grow through a cavity filled with fluid, for at the time of transplantation it seems that the somatopleure and splanchnopleure were still in contact, the body cavity not yet having been formed between them.

It would seem that these experiments should be interpreted as practically deciding in favor of the outgrowth theory, for the nerve-centre is shown to be the commanding influence in the development of the fibres. On the other hand the remarkable experiments of Braus [30] have been taken by their author to support Hensen's view. As these experiments are so original in their conception, and lead to otherwise very important results, even though their author's interpretation of them does not seem to me to be justified, a brief account of them will not be out of place here.

Braus transplanted limbs of very young tadpoles to various parts of the body of other individuals and studied the nervous system in the transplanted appendages. It was found that no matter where the limb was implanted, its peripheral nerves would develop normally as regards the distribution of the branches within the appendage itself, though these nerves would have abnormal connections in the host. For instance, a fore limb implanted in place of a hind limb, which had been removed, would develop into a typical fore limb, acquiring a complete system of peripheral nerves, normal in their arrangement, though derived from the lumbosacral plexus. A limb transplanted to the head might even acquire normal nerves derived, for instance, from the facial nerve. These nerves are not only normal as regards their arrangement, but they are also functional, for such transplanted limbs not only move in response to stimuli, but they may also exhibit spontaneous

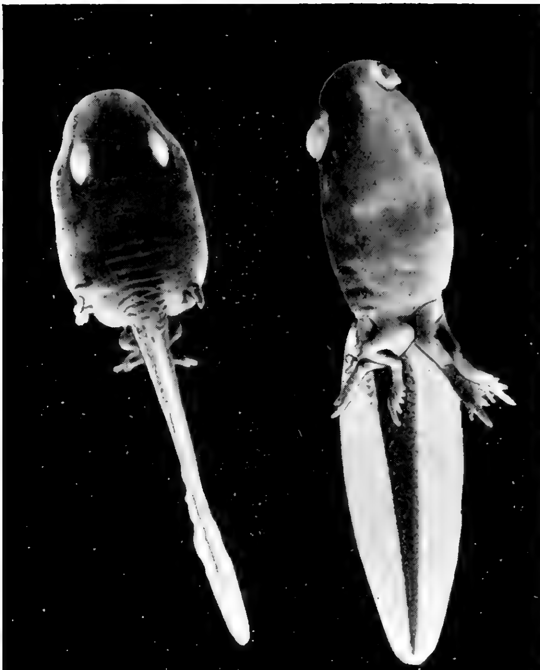


Fig. 13.—Two tadpoles with supernumerary transplanted limbs.

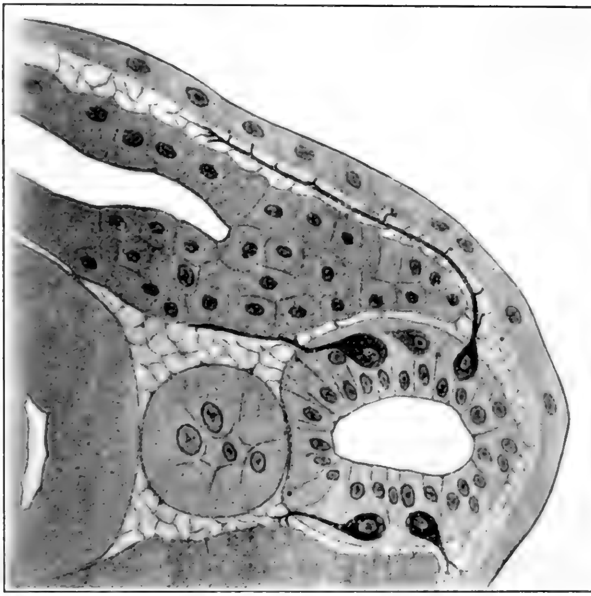


Fig. 14.—Semi-diagrammatic section through the spinal cord and adjacent organs of an axolotl embryo (after Held).

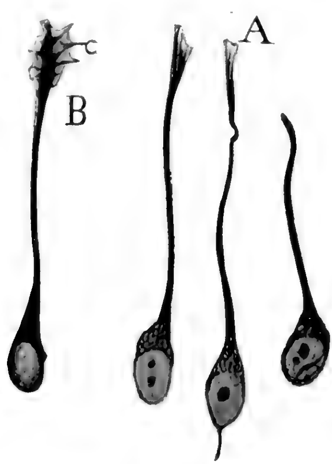


Fig. 15.—*A*, neuroblasts stained with silver nitrate; *B*, neuroblast impregnated by the Golgi method; *C*, growth cone. (After Ramon y Cajal.)

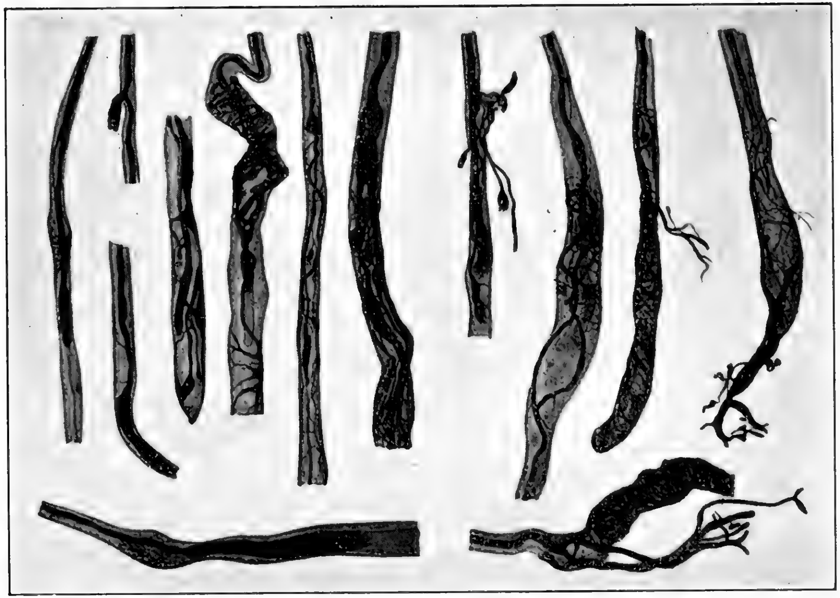


Fig. 16.—Regenerating nerve-fibres from the end of the central nerve stump of the sciatic nerve of a dog taken from six to forty-eight hours after cutting the nerve (after Perroncito).

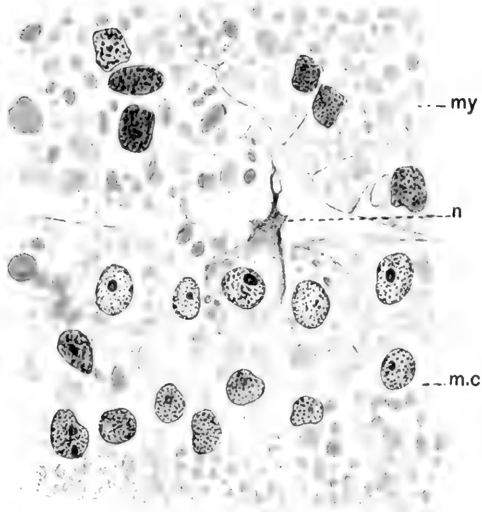


FIG. 17.—Portion of a horizontal longitudinal section through the spinal cord (*m.c.*) and portion of two muscle plates (*my*) of frog embryo. The cell (*n*) with the branched process is a neuroblast showing the first stage of the formation of the nerve-fibre.

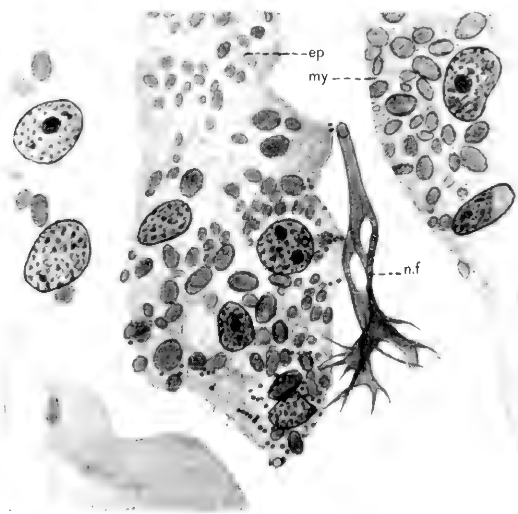


FIG. 18.—End of growing nerve-fibre (*n.f.*). From a sagittal section through a frog embryo slightly older than the one from which Fig. 17 is taken. The nerve-fibre is growing between the epidermis (*ep*) and the muscle plates (*my*).

movements. These fundamental facts are of extreme importance, though they do not answer in themselves the question at issue, for, either the beginnings of the nerves might themselves have been transplanted with the limb, as Hensen's view would postulate, or else the nerves might have grown in from the nerves of the host, being merely guided in their growth by the structures present in the transplanted part.

In order to decide this point, Braus conceived the very ingenious experiment of transplanting, instead of a normal limb, a limb-bud taken from a larva which had been deprived of its central nervous system at a very early age, and which had, in consequence, developed without any peripheral nerves. Braus found in his experiments that even when such a limb is implanted into a normal embryo, no nerves develop within it. In addition to this, he also found that when supernumerary appendages arise from normal transplanted limb-buds, as they do frequently by a process of twinning (Fig. 13), they are likewise devoid of nerves. From these results Braus inferred that within the peripheral parts of a developing organism there is normally some structure which is essential to the formation of the nerve-fibre, and which is destroyed when it is cut off for a time from its connection with the central nervous system. In other words, Braus concludes that the peripheral parts of an embryo do not merely serve to guide the nerves in their distribution, but that they actually contribute formed structures to build up the nerve-fibres.

Similar experiments which I made in the spring of 1906 upon other species of amphibians [31] show, however, that these results are not of general validity. In the case of the wood frog (*Rana sylvatica*) and the common toad (*Bufo lentiginosus*) it was found that the transplanted limbs, whether taken from normal or from nerveless tadpoles, would in the course of their development usually acquire a system of normally arranged nerves, and this was found to hold for the supernumerary as well as for the primary transplanted appendages. The individual cases showed considerable variation as regards completeness of innervation, but this condition could not in

any way be connected with differences in the origin of the limbs and could only be referred to slight accidental inequalities in the operations. Were there within the limbs any kind of preformed structures, which give rise to nerve-fibres, we should, according to Hensen's view, expect them to atrophy through disuse in nerveless individuals long before transplanting, as is actually the case with nerves that are already visibly differentiated. Indications that something was lacking in the nerveless limb would then be shown in the inability of the nerves to develop within it. But this is not the case, for the nerves do develop within such limbs just as in any normal appendage. The results of these experiments, instead of supporting Hensen's theory, add, therefore, further evidence against it.

Distinctly as all of the foregoing facts point to the correctness of the view that the nerve-fibre is formed as an outgrowth from the ganglion cell, there is still one defect in the conditions of experimentation which stands in the way of rigorous proof. The nerve-fibres have in all of the experiments developed within living tissues, and the possibility of the latter contributing organized material to the nerve elements has not been entirely excluded. This matter has again recently been taken up by Held [32] and Paton,[33] who have endeavored to show by the aid of exquisite histological methods that the protoplasmic bridges, found between the cells of the embryonic body, do actually take part in the formation of the nerve-fibres. Both of these investigators support, in other words, Hensen's view, although Held's conception is a distant modification of it, in the sense that it approaches measurably the outgrowth theory of His. According to Held the peripheral nerve-fibre does not grow out free into spaces between the cells, but it can grow only into the protoplasmic bridges or plasmodesmata which have already been formed by other cells. To translate his own words: "The nerve paths arise through the transformation of plasmodesmata into neurodesmata" (Fig. 14). Striking as Held's preparations are, it does not seem to me that they prove the essential nature of the protoplasmic bridges. In fact, it is not even proved that these so-called plasmodesmata are not to a considerable extent coagulation products; and even if they are actually

present in the living embryo just as seen in preserved specimens, their extremely fine structure would seem almost to preclude the possibility of distinguishing whether the nerve-fibres actually grow within them, or whether they entwine themselves amongst them as a vine growing upon a lattice.

That the material upon which Held bases his views is quite capable of another interpretation is evidenced by the fact that Ramon y Cajal,[34] who has studied the same question, upon similar material, making use of the same methods as Held, emphatically supports the outgrowth theory in its original form. The conclusions drawn from such preparations, however definite they may seem, appear, therefore, to be nothing more than a matter of interpretation.

In order to reach a final settlement of this question it thus became necessary to devise a method by which to test the ability of a nerve-fibre to grow outside the body of the embryo, where it would be independent of protoplasmic bridges. At first a number of futile attempts were made to cultivate pieces of embryonic nerve tissue in various physiological salt solutions and within the cavities of the normal embryonic body. It then seemed that the outgrowing nerve might be stereotropic, and hence unable to leave a solid mass of cells to grow into a perfectly fluid medium. As the most suitable solid medium in which it would be possible to envelop embryonic tissue and observe its subsequent development, fresh lymph was chosen, first, because the fibrin threads which are formed on clotting might simulate mechanically Held's "plasmodesmata," though they could not be supposed actually to transform themselves into the nerve-fibre; and, secondly, because the serum of the lymph would presumably afford a natural culture medium for the embryonic cells. Small portions of various tissues of the embryo were dissected out and removed by a fine pipette to a cover-slip upon which was a drop of lymph freshly drawn from one of the lymph sacs of an adult frog. The cover slip was then inverted over a hollow slide and sealed on with paraffin. These manipulations were carried out as far as possible under aseptic precautions. The lymph clots almost immediately and holds the transplanted tissue in place. The speci-

men can then be readily observed under high powers of the microscope from day to day.[35]

It has been found possible to keep such preparations alive for more than five weeks; and, during the first week at least, differentiation takes place in a manner characteristic of each tissue. Cells taken from the muscle plates differentiate into muscle-fibres with striated fibrillæ; and when small pieces of spinal cord with portions of the muscle plates attached are taken, twitching movements of the muscle-fibres may often be observed on the following days.

In order to understand the behavior of nervous tissue under the conditions just described, it will be well to examine for a moment the appearance of the end of a growing nerve-fibre as pictured by various authors from normal preserved specimens. In the figure by Held (Fig. 14) the nerve-fibre is seen to run out into a number of fine filaments, which are supposedly the protoplasmic bridges (plasmodesmata) between the cells. According to Ramon y Cajal [36] we find at the end of the growing fibre a swelling (*cône d'accroissement*), which has a few short processes extending out from it; such endings have been demonstrated both by the Golgi and the silver reduction methods (Fig. 15). In the regenerating fibre, as shown by Ramon y Cajal and by Perroncito [37] there is found a somewhat similar structure at the end of the axis-cylinder (Fig. 16). A nerve-fibre, which is just beginning its development, taken from a section of a normal frog embryo about 3 mm. long is shown in Fig. 17. We see a branched protoplasmic process extending out into the space between the two myotomes and the skin from a cell situated within the medullary cord. If we examine one of these same nerves in a slightly older embryo we find that it has become a fibre of some length, having at its end a structure (*n.f*) such as is shown in Figs. 18 and 19. Here there are several fibres bundled together, ending in a mass of hyaline protoplasm resembling a rhizopod with fine branched pseudopodia. These structures may be best seen in the fibres that arise from the dorsal giant cells of Rohon-Beard, and are well brought out by the ordinary embryological methods of fixation and staining.

Fig. 19.—End of growing nerve-fibre, as seen in section. Similar to fibre shown in Fig. 18.

Fig. 20.—Isolated cell from a piece of embryonic spinal cord growing in a drop of clotted lymph. The cell body, which is filled with yolk granules, is sending out a hyaline protoplasmic process which undergoes amœboid movements. Drawn from a live specimen.

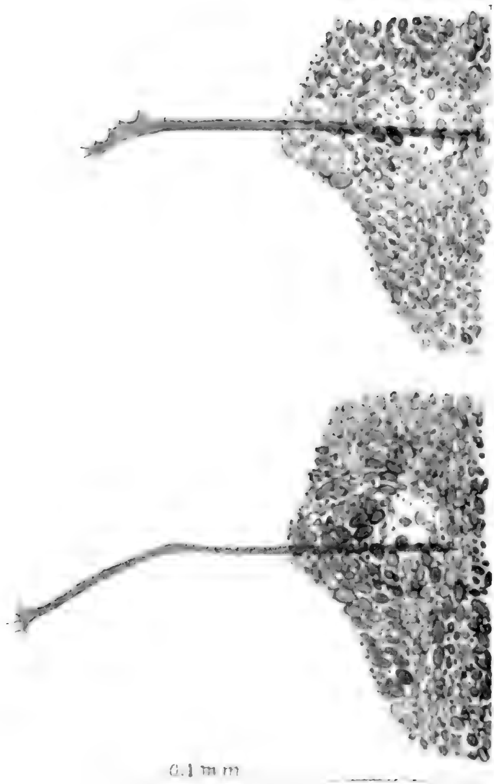


FIG. 21.—Two views, taken twenty minutes apart, of the same nerve-fibre growing from a group of embryonic spinal-cord cells in the lymph.

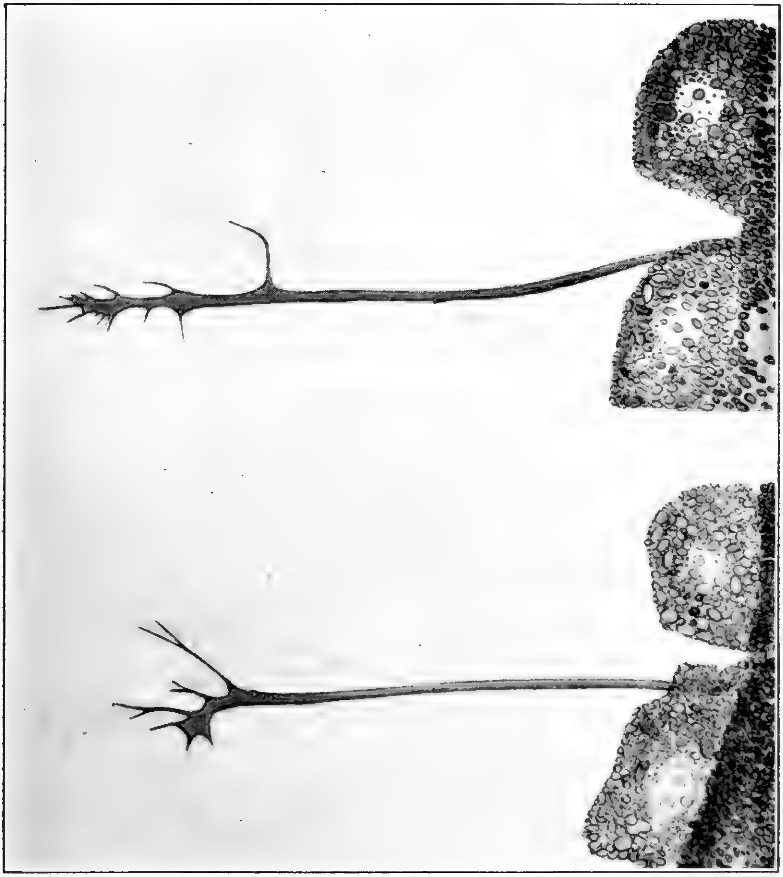


FIG. 22.—Two views of the same nerve-fibre taken fifty minutes apart. Preparation similar to that shown in Figs. 20 and 21.

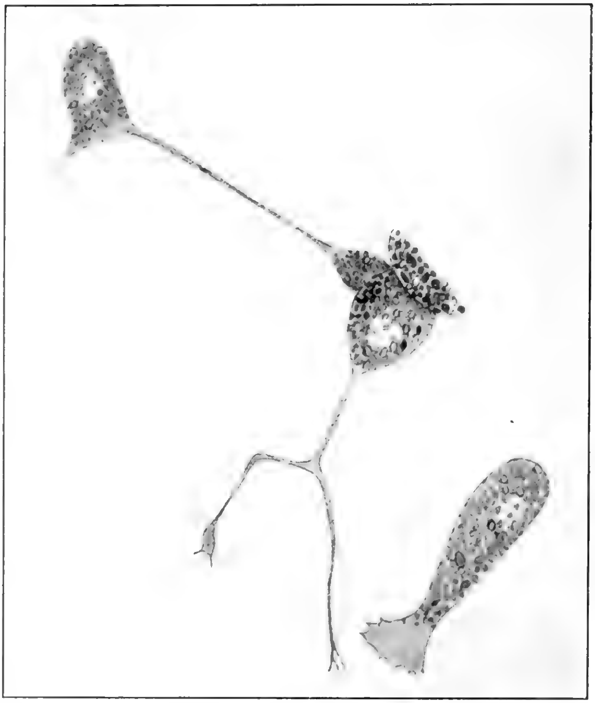


Fig. 23.—Isolated ganglion cell with branched nerve-process from tissue taken from the branchial sense organs of frog embryo. The preparation also shows a cell with a short process and twin cells joined by a hyaline protoplasmic fibre. From a live specimen in lymph.

Let us now observe how the nerve tissue under cultivation in the lymph behaves. It must be borne in mind that when this is taken from the embryo it consists entirely of rounded cells without any signs of differentiation into fibres. Examined after a day or two of cultivation, fibres are found in a considerable number of cases extending out from the mass of tissue into the lymph clot. An early stage of this development is shown in Fig. 20, which represents a cell that has become detached from the main mass of tissue. This cell is still gorged with food yolk, but at one pole it has sent out a hyaline protoplasmic process, which was observed to undergo distinct changes in form. Fig. 21 shows another case. Here the fibre proceeds from a mass of cells and its own particular cell of origin cannot be distinguished. The figure represents two stages of the same fibre sketched at an interval of twenty-five minutes, during which time the fibre has lengthened twenty microns. The case shown in Fig. 22 is a much larger fibre, about 3 microns in diameter, with much more protoplasm at the end. The movements of this fibre were extremely active, and the change of form with accompanying lengthening is well shown by comparing the two sketches, which were made fifty minutes apart.

Similar phenomena were observed in the case of pieces of ectoderm taken from the branchial region, which is known to give rise in part to the ganglia of the cranial nerves (Fig. 23). On the other hand, other tissues of the embryo do not give rise to such structures, though kept under exactly similar conditions. This holds for muscle plates, notochord, yolk endoderm, and ordinary ectoderm from the abdominal walls. All of these cells exhibit amœboid activity in a greater or less degree, though it does not result in the drawing out of the protoplasm into a filament. There can be no doubt, therefore, that the free-ending filamentous structures are specifically nervous, and when we see the exact morphological correspondence between them and the nerve-fibres in sections of embryos of the corresponding age, it becomes certain that the two things are the same.

The foregoing observations show beyond question that the nerve-fibre begins as an outflow of hyaline protoplasm from

cells situated within the central nervous system. This protoplasm is very actively amœboid, and as a result of this activity it extends farther and farther from its cell of origin. Retaining its pseudopodia at its distal end, the protoplasm is drawn out into a thread, which becomes the axis-cylinder of a nerve-fibre. The early development of this structure is thus but a manifestation in a marked degree of one of the primitive properties of protoplasm, amœboid activity. We have in the foregoing a positive proof of the hypothesis first put forward by Ramon y Cajal [38] and von Lenhossék,[39] who based it upon the consideration of the cones of growth found by the Golgi method at the end of the growing fibre.

At present we have but little evidence regarding the influences which bear upon the growing nerve, though now that its mode of growth is known with certainty, we may hope that further experiments will soon throw light upon the problem. From the fact that the nerve-fibre is capable of growing out into a lymph clot, and from other facts touched upon in the above discussion, it seems to be established that the mere act of extension is independent of external stimuli, or in other words, that it is due to properties that lie within the cell itself. On the other hand, we cannot escape the conclusion that within the body of the developing embryo there are many influences, exerted by the various organs and tissues, that guide the moving protoplasm at the end of the fibre and ultimately bring about the contact with the proper end organ. The experiments in transplanting limbs show, for instance, that we must seek in the limb itself for the factors which influence the distribution of the ingrowing nerve; for any nerve at all, in whose way a limb may be implanted, may enter the latter and become distributed in a manner normal for that limb. The shifting of parts during development is another factor of importance, as Hensen originally pointed out. For example, the lateral line nerve grows out and establishes its connection with the rudiment of its end organs at a time when its ganglion and the latter are very close together; and the enormous length that the nerve attains in the full-grown tadpole is due solely to the shifting of the sensory rudiment during development. Still, such crude

mechanical factors are by no means sufficient to explain the intricacies of the nervous system of a higher animal, and we must seek farther for more subtile influences, possibly such as tropisms, as originally suggested by Ramon y Cajal.* Very convincing evidence of chemotropic influences has already been found in the case of regenerating nerves by Forssmann,[40] who showed in a most ingenious manner that degenerating nerve tissue would attract the regenerating fibres. How far such influences and how far mechanical stimuli determine the course of the nerve-fibre in embryonic development can only be determined by experiment. It is to be hoped that the method of isolation as described above will here yield results of value.

As regards the theories of nerve development that have been the subject of the foregoing argument, I need scarcely point out that the experiments now place the outgrowth theory of His upon the firmest possible basis,—that of direct observation. The attractive idea of Hensen must be abandoned as untenable. The embryological basis of the neurone concept thus becomes more firmly established than ever.

REFERENCES.

[1] For a full account of Born's work see Archiv für Entwickelungsmechanik, Bd. iv, 1896–7. For a general account of the subject of embryonic transplantation see the admirable address of Spemann before the Versammlung Deutscher Naturforscher und Aerzte in Stuttgart, 1906; also Spemann, Zum Problem der Correlation in der tierischen Entwicklung, Verh. d. Deutschen Zool. Gesellschaft, 1907; Braus, Propfung bei Tieren, Verh. d. Naturhist.-medizin. Ver. z. Heidelberg, Bd. viii.

[2] Archiv für Entwickelungsmechanik, Bd. vii, 1898.

[3] Archiv für Mikroskopische Anatomie, Bd. lxiii, 1903.

[4] The Journal of Experimental Zoölogy, vol. iv, 1907.

[5] Verhandlungen der Deutschen Zoologischen Gesellschaft, 1906.

[6] The Journal of Experimental Zoölogy, vol. iii, 1906, and vol. iv, 1907.

[7] American Journal of Anatomy, vol. iii, 1904; and the Journal of Experimental Zoölogy, vol. ii, 1905.

---

* In the course of the experiments here described, small pieces of tissue taken from the muscle plates or from the epidermis were in a number of cases placed in the drop of lymph along with the nervous tissue. It was hoped to find by this means evidence of attraction or repulsion exerted by these tissues upon the growing nerve-fibres. No definite results, however, have as yet been obtained from these experiments.

[8] Mikroskopische Untersuchungen, 1839.
[9] Development of Elasmobranch Fishes, London, 1878.
[10] Mitteilungen aus der Zoologischen Station zu Neapel, Bd. x, 1891.
[11] Mitteilungen aus der Zoologischen Station zu Neapel, Bd. xii, 1897.
[12] Allgemeine Anatomie und Physiologie des Nervensystems, Leipzig, 1903.
[13] Archiv für Mikroskopische Anatomie, Bd. lxvi, 1905.
[14] Archiv für Anatomie und Physiologie, Anatomische Abtheilung, 1886.
[15] Anatomischer Anzeiger, Bd. v, 1890.
[16] Anatomischer Anzeiger, Bd. vii, 1892.
[17] Archiv für Mikroskopische Anatomie, Bd. lvii, 1901.
[18] Sitzungsberichte der Niederrheinischen Gesellschaft für Natur- und Heilkunde zu Bonn, 1904; American Journal of Anatomy, vol. v, 1906.
[19] Mittheilungen aus der Zoologischen Station zu Neapel, Bd. xviii, 1907.
[20] Journal of Experimental Zoölogy, vol. iv, 1907.
[21] Anatomischer Anzeiger, Bd. xxvi, 1905.
[22] Archivio di Anatomia e di Embriologia, vol. iv, 1905; Anatomischer Anzeiger, Bd. xxviii, 1906.
[23] Virchows Archiv, Bd. xxxi, 1864; Archiv für Mikroskopische Anatomie, Bd. iv, 1868; Zeitschrift für Anatomie und Entwickelungsgeschichte, Bd. i, 1876; Die Entwickelungsmechanik der Nervenbahnen im Embryo der Säugetiere, Kiel und Leipzig, 1903.
[24] Trans. Roy. Soc. Edinburgh, vol. xli, 1904.
[25] Archiv für Mikroscopische Anatomie, Bd. lxvi, 1905.
[26] Mittheilungen aus der Zoologischen Station zu Neapel, Bd. xviii, 1907.
[27] Verhandlungen der Anatomischen Gesellschaft, 1906.
[28] American Journal of Anatomy, vol. v, 1906.
[29] American Journal of Anatomy, vol. vi, 1907.
[30] Anatomischer Anzeiger, Bd. xxvi, 1905.
[31] The Journal of Experimental Zoölogy, vol. iv, 1907.
[32] Verhandlungen der Anatomischen Gesellschaft, Rostock, 1906; Anatomischer Anzeiger, Bd. xxx, 1907.
[33] Mittheilungen aus der Zoologischen Station zu Neapel, Bd. xviii, 1907.
[34] Anatomischer Anzeiger, Bd. xxx, 1907; Bd. xxxii, 1908.
[35] Proceedings of the Society for Experimental Biology and Medicine, 1907.
[36] Anatomischer Anzeiger, Bd. v, 1890; Bd. xxx, 1907; and Bd. xxxii, 1908.
[37] Zieglers Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie, Bd. xlii, 1907.
[38] La Rétine des Vertébrés, La Cellule, T. ix, 1893.
[39] Der feinere Bau des Nervensystems im Lichte neuester Forschungen, Berlin, 1895.
[40] Zieglers Beiträge zur pathologischen Anatomie und zur allgemeinen Pathologie, Bd. xxiv, 1898, and Bd. xxvii, 1900.

ARTIFICIAL RESPIRATION IN MAN *

PROF. E. A. SCHÄFER,
University of Edinburgh.

IT has been said that "Science is measurement." If this definition does not apply to all sciences, it is at least pregnant with meaning in physiology. And to no branch of physiology does the definition of science as measurement more directly apply than to that which deals with the respiratory exchanges of the body.

For the purpose of measuring the volume of air which is inspired and expired the classical instrument is the *spirometer;* this has been employed in one form or another by all who have carried on investigations upon this subject. The particular form which the instrument usually takes in the laboratory and consulting room is that which was devised by Hutchinson.[1] Hutchinson's spirometer is, however, defective in one point, viz., that the inner cylinder, into which the air is passed, is not equally balanced at all points of its immersion in the water which is contained in the outer cylinder. This defect was made good by Marcet,[2] by the introduction of a secondary counterpoise. This works from a cam-like projection attached to the pulley over which the cord carrying the main counterpoise passes. This cam is so arranged that the secondary counterpoise exerts more leverage the more the inner cylinder of the spirometer becomes lifted out of the water as air passes into it; and in this manner the increased weight of the moving cylinder is, more or less exactly, compensated. Without some such arrangement the inner cylinder will be exerting more pressure upon the contained gases the more it is raised from the water, and the register of volume at different levels will therefore be unequal.

---

* Lecture delivered May 9, 1908.

The first observer to attempt to determine the amount of air entering and leaving the lungs in ordinary respiration—the tidal air, as it is customarily called—appears to have been Borelli [3] in the seventeenth century. Borelli was followed a century later by Jurin [4] and several other investigators, mostly British, including Dalton, Humphry Davy, and Abernethy. But the most numerous and precise observations upon this subject were those of Vierordt [5] and Hutchinson [1] about the middle of the last century—both of whom also collected the results obtained by previous investigators.

The main outcome of all these measurements was to show that there is an enormous individual variation in the amount of tidal air. The variations depend, as Hutchinson shows, upon age, sex, stature, physical development, and conditions of rest and exercise. More than anything do they depend upon the natural rhythm of respiration in the individual, the amount of tidal air being in inverse relation to the rate of breathing. Thus Marcet in two men (of short stature) whose normal rate of respiration was 16 per minute obtained as an average measurement of the tidal air (the result of 210 experiments) 250 c.c.; whereas Speck, in an individual with a respiratory rhythm of 6.3 per minute, found a tidal-air volume of more than a litre. The extremes are, however, much more than this, the numbers given by Hutchinson, collected by him from different sources, being from 49 c.c. to 1640 c.c. His own results in 80 observations varied from 114–196 c.c. during rest, and 262–360 c.c. during exercise; but the rate in all these cases is not furnished.

Much more important is it from the physiological point of view to determine the amount of air respired per minute or in any other definite time. If this is done it is still found that there is great individual variation. This is indeed to be expected from the differences of stature and physical development which prevail. But the variations are in no way comparable to those which are found for single respirations. Vierordt, as the result of numerous measurements, obtained an exchange per minute of about 5300 c.c. An individual with a respiratory rhythm of 12 per minute would therefore inhale and exhale

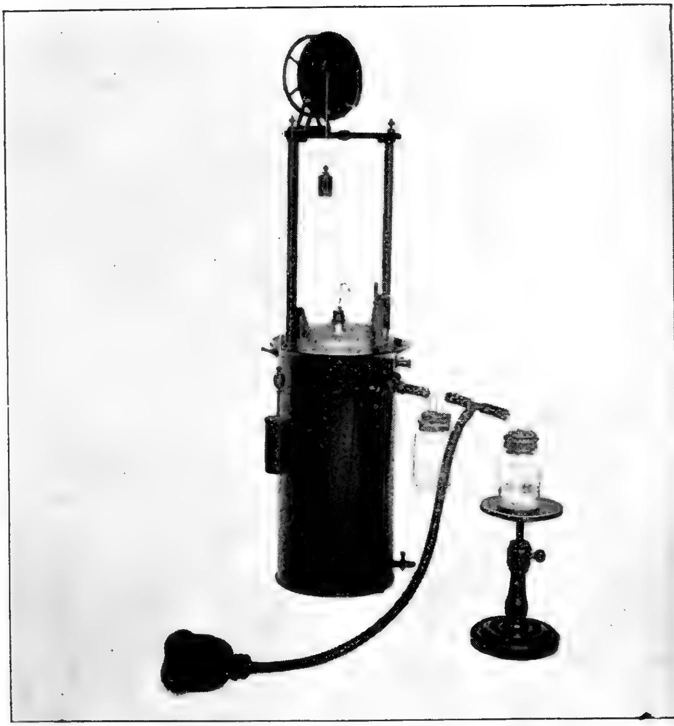


Fig. 1.—Hutchinson's spirometer as modified by Marcet (see also Fig. 11). (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

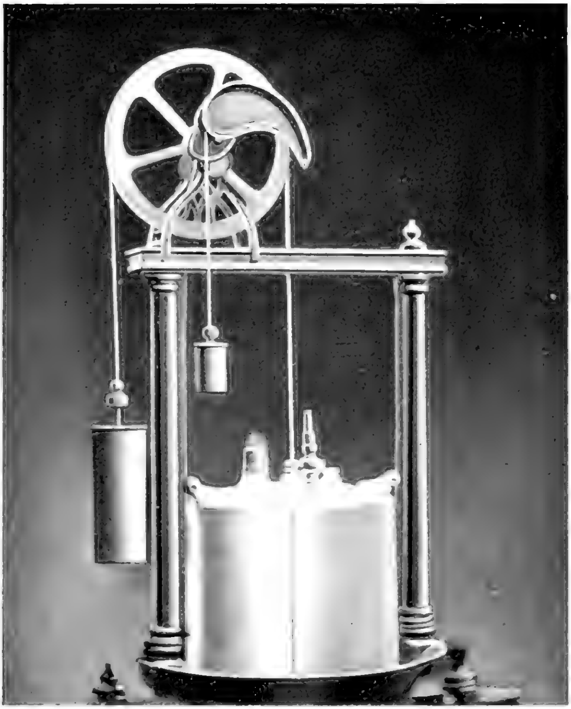


FIG. 2.—Cam with small weight for balancing spirometer cylinder in all positions. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

with every respiration about 440 c.c. of air. From this we deduce the fact that if we desire to replace natural respiration by artificial we must be prepared to drive air in and out of the lungs to about this extent with each respiration, that is, if we pump at the rate of about 12 per minute or once in 5 seconds. And any method of artificial respiration which fails to attain this standard or to pump air in an amount less than about 5300 c.c. per minute must be regarded as failing to fulfill the purpose for which it is employed.

In the year 1890 the Royal Medical and Chirurgical Society of London appointed a committee to investigate the relative efficiency of the current methods for performing artificial respiration, especially in cases of drowning. The committee was composed of a small number of medical and scientific men; but of those who were appointed only two, besides myself, took an active part in the experiments which were instituted to determine the question, these being both well-known London surgeons, Mr. Pickering Pick of St. George's Hospital and Mr. Henry Power of St. Bartholomew's Hospital. Our experiments were made upon the cadaver; and many an hour did we spend in the dead house in the futile endeavor by one method or another to obtain an air-exchange in any way approaching that which may be considered the normal. Obviously subjects with chest and lungs perfectly healthy had to be selected, and this eliminated most which were offered to us. But even in the normal subject the difficulty which the rigidity of the cadaver presents was practically insuperable, at least by the methods with which we were then acquainted, viz., the Marshall Hall, Silvester, and Howard.

For this reason we gave up further attempts to obtain results in this way, but not before we had induced Dr. J. S. Bolton, then resident physician of the large Asylum at Claybury, belonging to the London County Council, to institute similar experiments—opportunities for which were naturally frequent, he himself being on the spot. Dr. Bolton met with no greater measure of success; and we decided to turn our attention to another method of experimentation, viz., upon the living

subject. For it was evident to us that it would be necessary to re-investigate the phenomena attendant upon drowning, and for this purpose to institute experiments on animals, an examination of the literature of the subject having revealed up to that time very few experimental investigations which had been carried out by modern graphic methods. Such investigations are however essential in order to determine precisely the changes in the circulation and respiration (especially as regards the time relations) which are produced in the process of drowning, as well as to ascertain the most appropriate method for the resuscitation of drowned animals. About this time I was leaving London for Scotland, and the work was accordingly transferred to my laboratory in Edinburgh. Here I had the advantage of the co-operation of Dr. Percy T. Herring, who carried out along with me the experiments upon animals, while those upon man were executed in conjunction both with Dr. Herring and my other assistants, as well as with others who were working at the time in my laboratory.

We selected dogs as the most fitting subjects of the experiments upon the effects of drowning—chiefly because they, of all the ordinary laboratory animals, possess a thorax and exhibit respiratory movements which most nearly approach in character to those of man. Our purpose was (1) to investigate the physiological phenomena manifesting themselves as the result of entrance of water into the air-passages and lungs, (2) to determine the time after complete cessation of respiration at which it might be possible to effect resuscitation by artificial means, (3) to discover the best means in the dog of carrying out artificial respiration.

Most of the animals were completely anæsthetized during the whole process, either with chloroform or ether, sometimes with the addition of morphine. One or two control experiments—made without anæsthetics—sufficed to indicate that the physiological phenomena are not materially modified by the anæsthetic, the chief difference being that without it there is great primary excitement and longer inhibition of respiration at the commencement of the immersion. In some cases the

drowning was effected by submersion of the whole animal or of the snout alone, in others by dipping a tube tied into the trachea into water. In most experiments the amount of water which was sucked in and absorbed was measured. It was found to vary greatly—from 75 c.c. to 690 c.c. This did not depend on the size of the animals—which varied in weight from 5½ kilograms to nearly 22 kilograms—for one of the smallest took in 385 c.c. during a submersion of the tracheal tube lasting 3 minutes, 30 seconds, while a large collie weighing 16 kilograms took in during the same time only 110 c.c., and the largest of all, a retriever weighing 21.8 kilograms, absorbed no more than 75 c.c. We further found that the possibility of recovery by artificial respiration after complete drowning was not related to the amount of water taken in. This water, if the animal be promptly removed from the water as soon as drowned, is not found in the lungs to any extent; it is absorbed into the blood nearly as fast as it is taken in. The specific gravity of the lungs under these circumstances is no greater than normal, while the blood shows distinct evidence of dilution. There is some, but not much more water in the lung tissue than in a normal animal killed by chloroform. The water-logged condition of the lungs which is usually described as present in cases of drowning is of course due to the fact that most of such cases have remained in the water some time after death and the interior of the lungs is the whole time in free communication with the water through the air-passages.

The physiological phenomena of drowning are a form of the phenomena exhibited in all cases of asphyxia. They are, however, modified by the reflex effects of the contact of the water with the sentient surfaces of skin, larynx, and air-passages; and these show themselves most markedly by a primary inhibition of respiration, which commonly occurs, as well as by an early and persistent tendency to cardiac inhibition. The reflex effects are somewhat masked by an anæsthetic, but with light anæsthesia are quite apparent. Even with deep anæsthesia the cardiac inhibition is well marked, although the inhibition of respiration may not be visible; but the respirations are

always slowed. Contact of water with the air-passages has another effect; it leads to an increased secretion of mucus. This mucus is apt to become churned up along with the water and air by the violent efforts at breathing into a froth, which within smaller air-passages may present an insuperable obstacle to the passage of air into or out of the alveoli and render futile any attempt at artificial respiration. Incidentally I may mention that the formation of such a froth is not peculiar to drown-

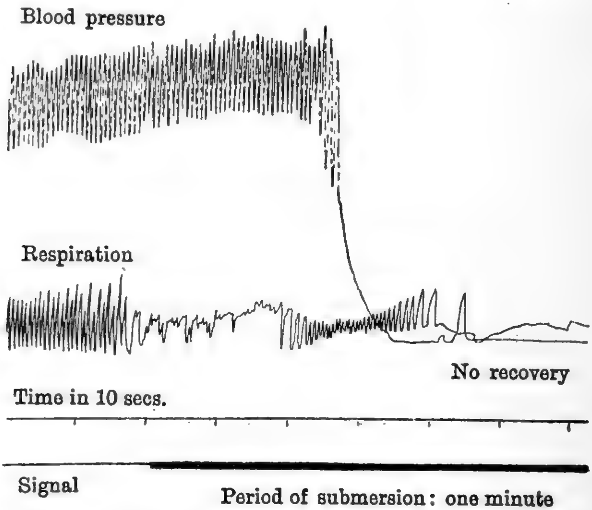


Fig. 3.—Dog: anæsthetized with chloroform. Drowned by submersion of snout under water. The experiment illustrates the rapidity with which, in some cases of drowning, death may occur from sudden and persistent cardiac inhibition. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

ing, although most often described in drowning cases. I have seen it as the result of ether administration alone; and its formation, and the accumulation of mucus, even without froth, may lead to dangerous symptoms in ordinary surgical anæsthesia. Such a result can be prevented by the prior administration of a small dose of atropine hypodermically; and since this also prevents the cardiac inhibition which is frequently produced by an anæsthetic—especially by chloroform—an atropine injection should in my judgment be part of the routine treatment in all operations which involve the use of a general anæsthetic.

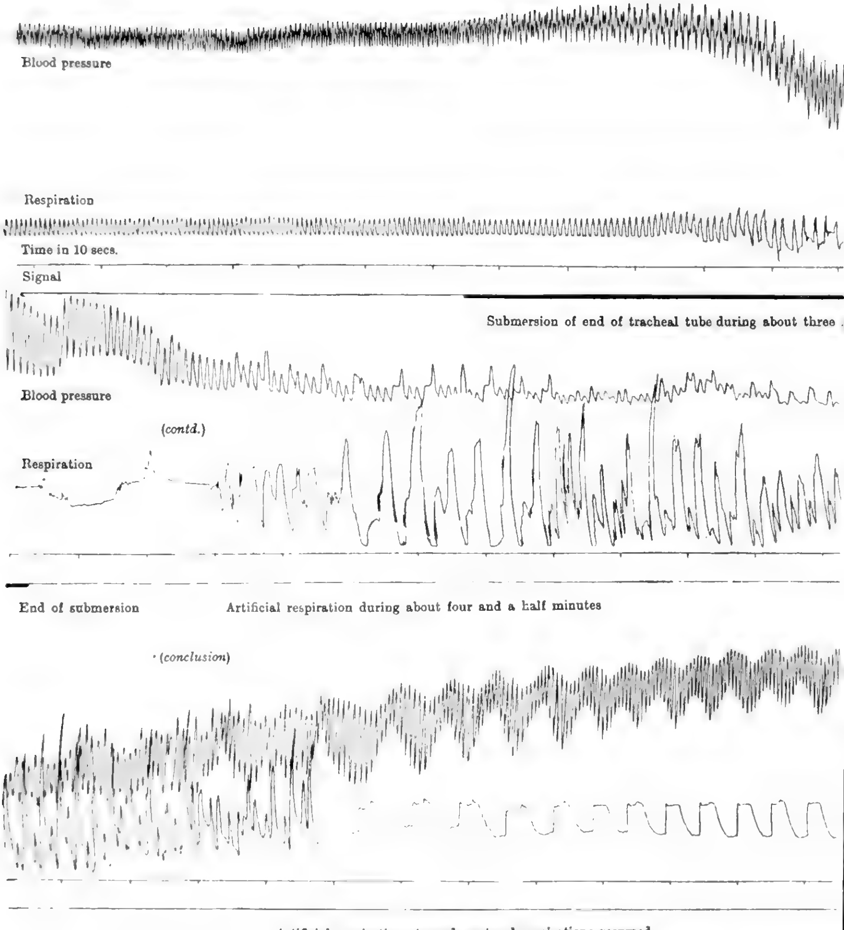
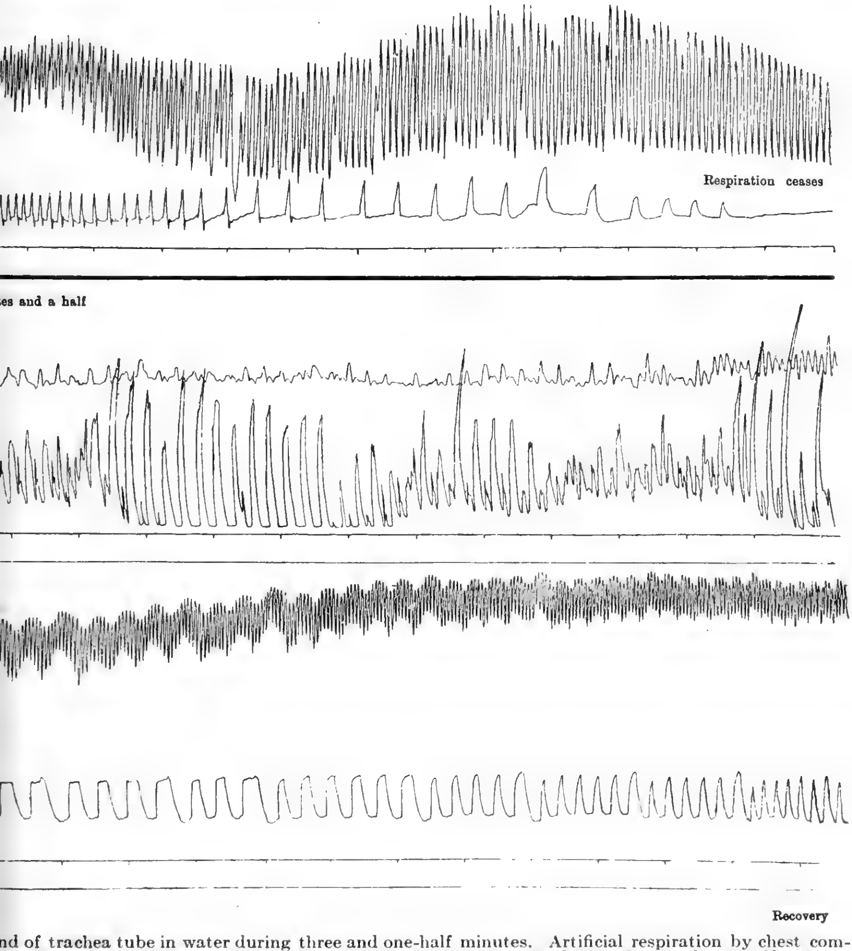


FIG. 4.—Large dog: anæsthetized with ether. Tube in trachea. Drowned by submersion of o
pression, which not only gives a respiratory tracing but also shows the effect of compression upon
natural respiration is resumed at first very slowly. During recovery the blood-pressure is graduall



nd of trachea tube in water during three and one-half minutes. Artificial respiration by chest com-
nert heart. After three minutes the heart begins to beat again and after four and one-half minutes
ng. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv).

The accompanying tracings (Figs. 3 to 10, see Plates) exhibit the most common phenomena relating to the respiration and circulation. These show much the same phenomena, whether the drowning were effected by immersion of the animal or by submersion of a tube tied into the trachea. There are, it will be seen, great individual differences in the effects produced both on circulation and on respiration. With regard to the respiration the following points are noticeable:

1. The initial cessation (holding of the breath), which may last some 20 seconds (Figs. 3, 6, 8).

2. When resumed the respirations are slow and may be irregular, but are deeper than normal and tend to increase in depth and slowness as asphyxia progresses. They are sometimes moderately slow and regular for a minute or two and then become much slower; usually they cease somewhat abruptly (Figs. 6, 7, 9, 10).

3. The total cessation of respiration takes place a variable time after immersion—sometimes in less than 2 minutes (Figs. 3, 8, 10), sometimes not until 5 or 6 minutes but usually in about 3 or 4 minutes (Figs. 4, 9)—during these times water is being passed in and out of the air-passages.

The character of the respiration varies much without apparent cause. In some experiments it is quite steady and equable (Fig. 9), in others irregular and convulsive (Fig. 8); but even in these, after the first excitement is over, it is invariably slow. Two or three minutes after complete cessation of respiration there may be a temporary resumption of respiratory movements in the form of a "staircase" group composed of a dozen or more regular and somewhat slow respirations (Fig 9). These may occur before the cessation of the heart beats, or after the heart has stopped. It is difficult to give an explanation of this phenomenon; there can be little doubt that by this time the respiratory centre is paralyzed. Tentatively I would suggest that these respirations are brought about by a tendency to rhythmic action at the lower neuromuscular level; but I admit that it is not easy to say why the cells and fibres at this level should not also be paralyzed by excess of carbon dioxide or lack

of oxygen. None of our animals recovered spontaneously as a result of these penultimate respirations; but it is conceivable that if the subject were promptly removed from the water and the air-passages became clear of water these respirations might serve to initiate recovery.

With regard to the circulation, the prominent features are:

1. A preliminary fall of arterial pressure mainly due to cardiac inhibition (Figs. 4, 5, 6, 9, 10). But since the fall is sometimes seen before there is any sign of cardiac inhibition, vasodilatation must also be a factor.

2. An arrest of this fall, followed, in spite of greatly increased inhibition, sometimes by an actual rise of pressure, the arterioles constricting (Figs. 6, 9). The marked rise of blood-pressure which characterizes asphyxia from closure of the trachea is absent in drowning.

3. A final fall of pressure with increased slowing of the heart-beat (Figs. 5, 6, 8). Sometimes this is accompanied by a gradual weakening of the beat (Fig. 4); in these cases the blood-pressure falls steadily, coming down nearly to zero; the heart continuing to beat, with less and less force, for one or two minutes, in certain instances for two or three minutes, in one case for as long as four and a half minutes, after cessation of respiration. At other times the beat of the heart does not undergo any appreciable weakening, but after beating slowly for a short time suddenly stops in a condition of complete inhibition (Figs. 6, 9). This may occur either simultaneously with the cessation of respiration or very soon after. In one instance this sudden inhibition was produced after one-half a minute's immersion (Fig. 3); the respirations were continued at a rapid rate for 20 seconds longer. In this case the animal was anæsthetized with chloroform and the tendency to inhibition was probably exaggerated by that drug. After section of the vagi (Fig. 10) or administration of a small dose of atropine this inhibition does not occur and the heart will then usually continue to beat considerably longer. Without atropine the utmost time after the commencement of submersion that we have found the heart continue to beat in the dog has been 10 minutes.

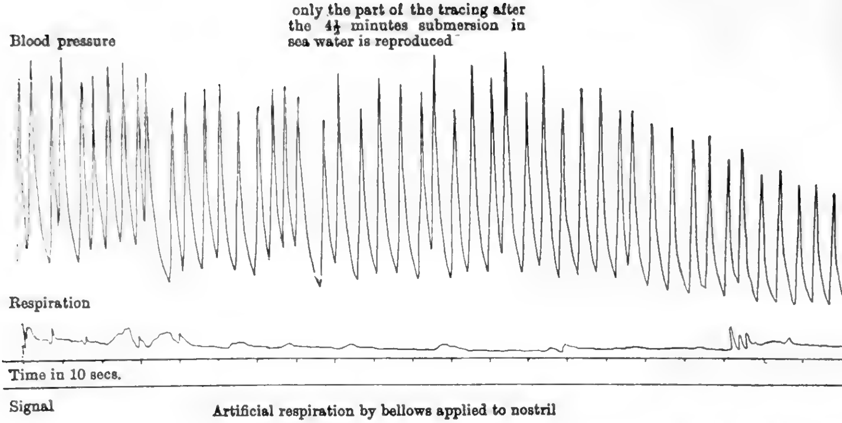


FIG. 5.—Dog: anæsthetized with chloroform. Snout submerged in sea water during four and one-
ration by applying a bellows to one nostril, the other being left open. This was begun three minutes a
natural respiration recommenced, and after another minute or two the heart and blood-pressure rapid

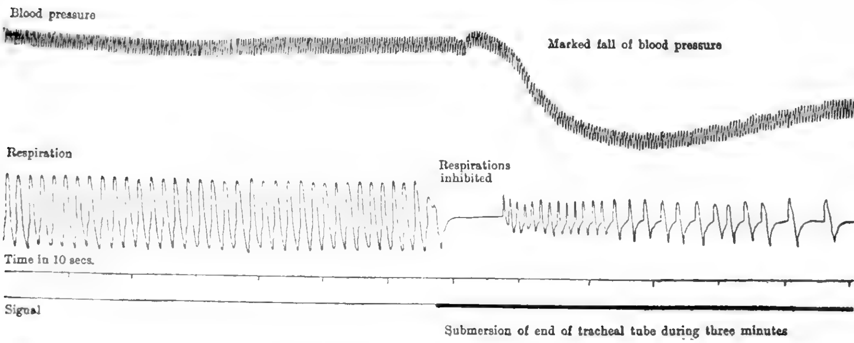


FIG. 6.—Dog: anæsthetized with ether. Tube in trachea. Submersion of end of tube in water du
of quiet respiration succeeded by slow but deep and convulsive respirations, (3) abrupt cessation of r
cardiac inhibition, (3) gradual rise of pressure with gradually increasing cardiac inhibition, (4) mark
cessation of respiration. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

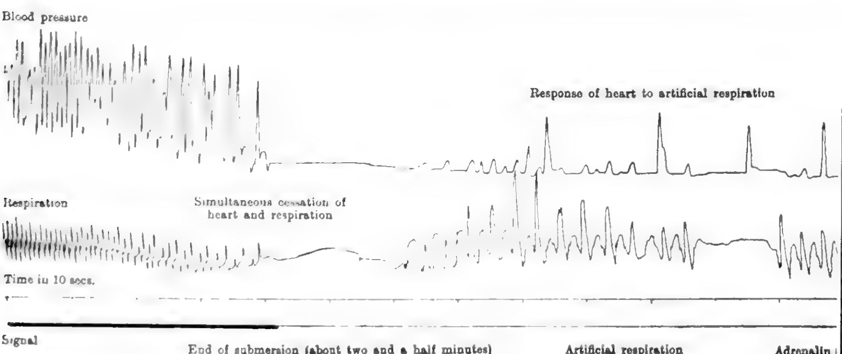
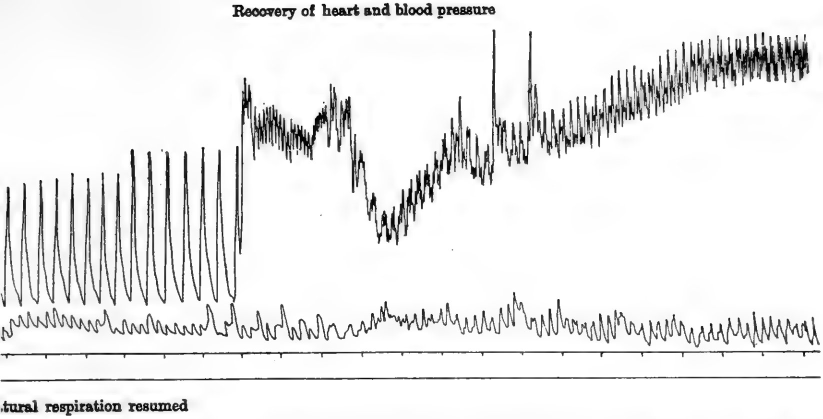
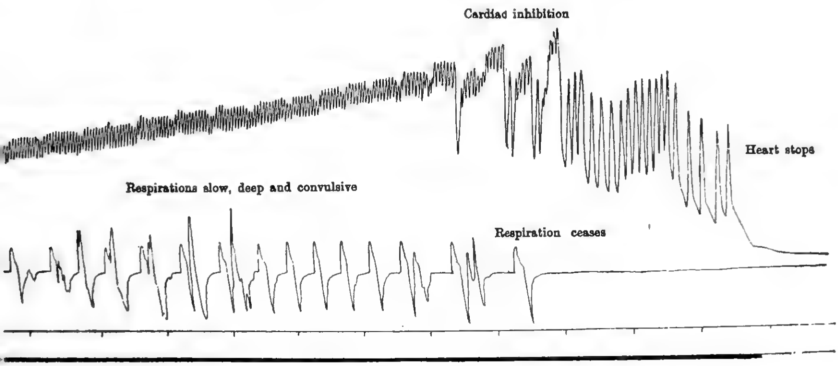


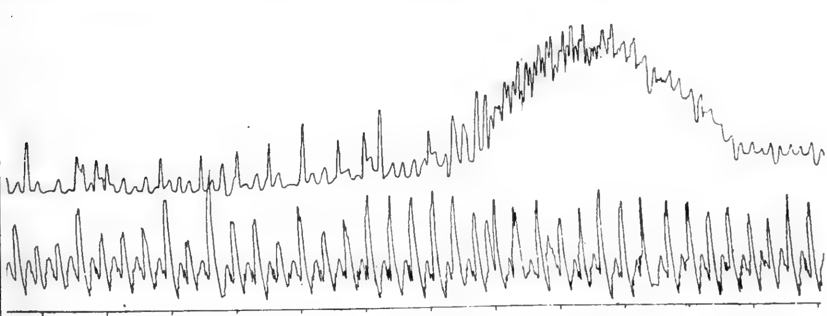
FIG. 7.—Large dog: anæsthetized with ether and chloroform. Only the end of the experiment is
respiration ceased simultaneously. Silvester method of artificial respiration employed, combined with
upon the heart and vessels. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)



minutes. After respiration had ceased, the heart continued to beat very slowly. Artificial respi-
removal from the water, the heart still beating slowly. After two minutes of artificial respiration,
ecovered. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)



; three minutes. The respiratory tracing shows (1) short period of respiratory inhibition, (2) period
rations. The blood-pressure tracing shows (1) slight initial rise, (2) rapid fall of pressure without
ardiac inhibition with fall of pressure, (5) sudden cessation of heart beat, half a minute after the



wn. Submersion of end of tracheal tube during about two and one-half minutes, when heart and
rapleural injection of adrenalin. No recovery, although the adrenalin produced a temporary effect

The most effective method of resuscitating the animals after drowning was found to be compression of the thorax and abdomen either in the supine or in the prone position. But in the former case we occasionally observed on post-mortem examination that we had ruptured the liver and produced extravasation of blood into the abdominal cavity. This is an accident that may easily happen in asphyxia from drowning, for we invariably noticed that after drowning the liver is enormously congested and enlarged and projects well below the margin of the thoracic cage. It is, moreover, an accident which has been known to occur in the human subject after employment of artificial respiration in the supine position.

We found great variability in the results of artificial respiration after drowning in the dog, even when the method employed was calculated to exchange a normal amount of air. As a general rule if respiration has just ceased and the heart is still beating steadily, artificial respiration will restore life. But if the heart stops simultaneously with the respiration or suddenly ceases soon after, the prospect of recovery is smaller. In this respect the results of artificial respiration in cases of drowning are closely similar to those in chloroform poisoning, which may be attended by an acute cardiac inhibition which is practically irrecoverable.

Another point which was accentuated in these experiments is the limited time after cessation of natural respiration within which artificial respiration is likely to be effective. In our dogs, if we allowed more than two minutes to elapse after the natural respiration had ceased, we almost always failed to obtain recovery even if the heart were still beating. The time therefore at one's disposal for resuscitation of a drowned subject is measured out in small fractions of a minute; and it is no exaggeration to say that every second is of importance, and that no time should be employed in loosening clothing or in any preliminary operation, but that in all cases artificial respiration should be commenced without one instant's delay.

Let us next consider the methods which have been at various times practised with the view of promoting the resuscitation of asphyxiated and especially of drowned persons.

The first systematic attempt to deal with this subject was that of Dr. Marshall Hall. In a paper published in 1857 entitled "Prone and Postural Respiration in Drowning," he describes the method which has since been known by his name. The essence of this consists in altering the lie of the subject from a lateral to a prone posture, the supposition being that with these changes in the position of the body would be produced alterations in the capacity of the thorax, the front of which, in the prone position, would sustain the weight of the trunk and would thus be somewhat compressed, while in the lateral position the more movable front of the thorax would be relieved of pressure and would tend to resume its original volume by virtue of its elasticity. It should be added that the weight of the trunk is in this method assisted in the task of forcing air out from the thorax by pressure between the shoulder blades when the body is in the prone position, and it may further be added that this pressure tends considerably towards the efficiency of the method.

Marshall Hall's method was adopted in England by the Royal Humane Society and by the National Life Boat Institution and was, and still is, taught and practised by both these bodies, and has also until lately been the common method employed in the Royal Navy.

In the following year (1858) Dr. H. R. Silvester—who died in London the other day at the age of 80—published in the *British Medical Journal* an article entitled "The True Physiological Method of Restoring Persons Apparently Drowned or Dead." Dr. Silvester came to the conclusion that the proper way to perform artificial respiration is to imitate as nearly as may be the natural movements, and especially the raising of the ribs. With this object he advocated the pulling of the arms forcibly above the head, thereby dragging upon the ribs by means of the pectoral and other muscles passing between the arm and the thorax and so effecting an enlargement of that cavity by the elevation of the ribs. Expiration in this method is brought about by lowering the arms again to the sides and then compressing the thorax laterally. By this mechanism it

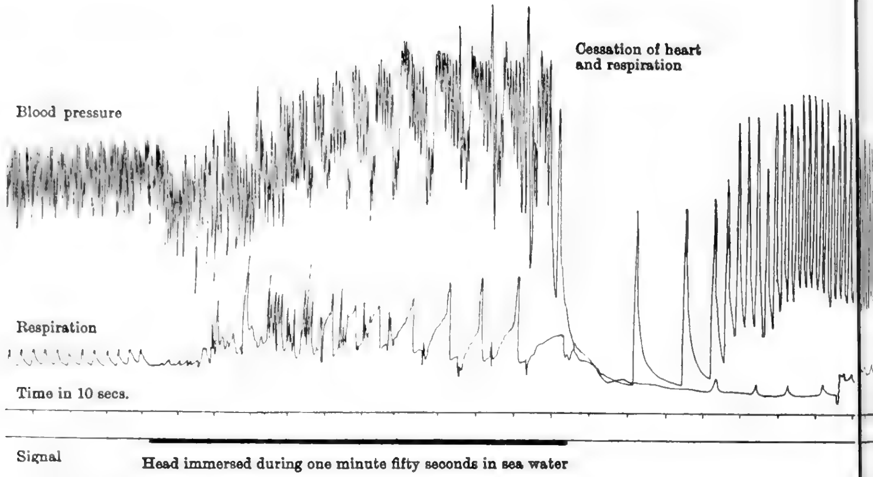


FIG. 8.—Dog: lightly anæsthetized with chloroform. Snout submerged during one minute fifty s
again after removal from the water. Simultaneous cessation of heart and respiration, with spontane
for some time. The curve of blood-pressure is very similar to that obtained by electrical excitation o

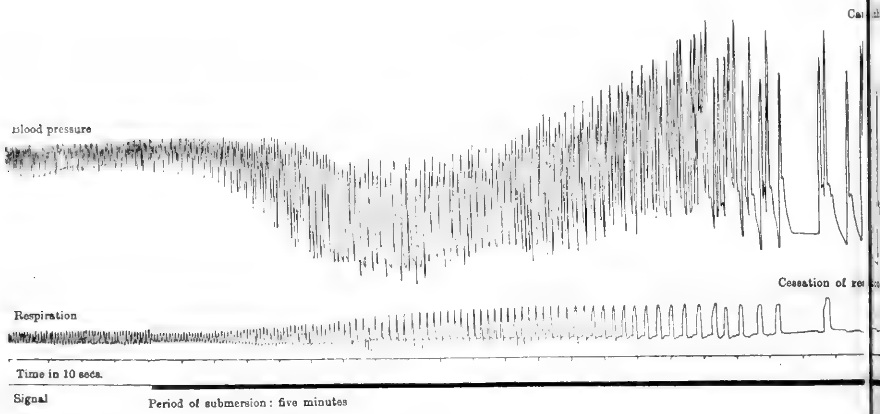


FIG. 9.—Dog: anæsthetized with chloroform. Tube in trachea submerged during five minutes in
become gradually slower and deeper and eventually stop abruptly two minutes before the heart ceases
The blood-pressure curve shows at first a fall and subsequently a rise, in spite of continued cardiac inl
Edinburgh, vol. xxv.)

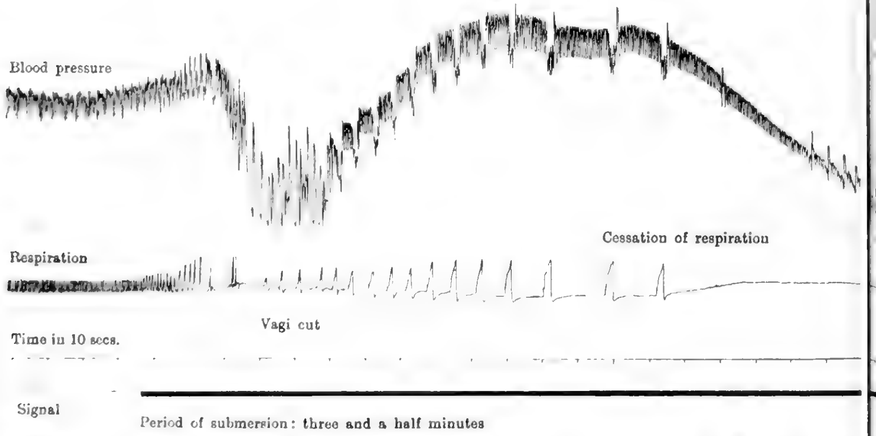
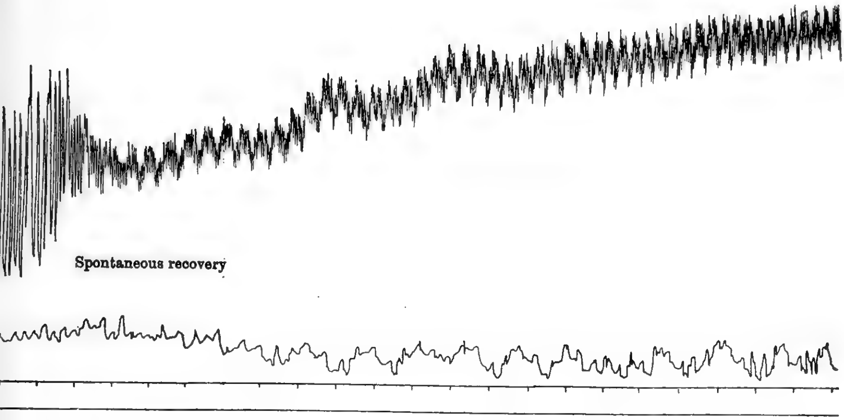
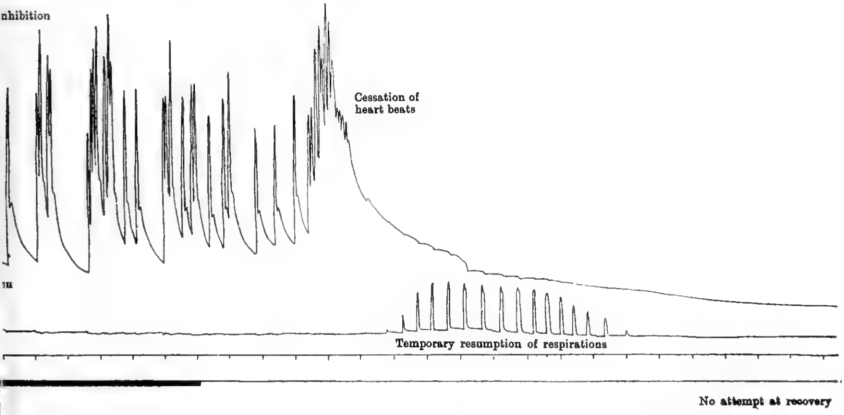


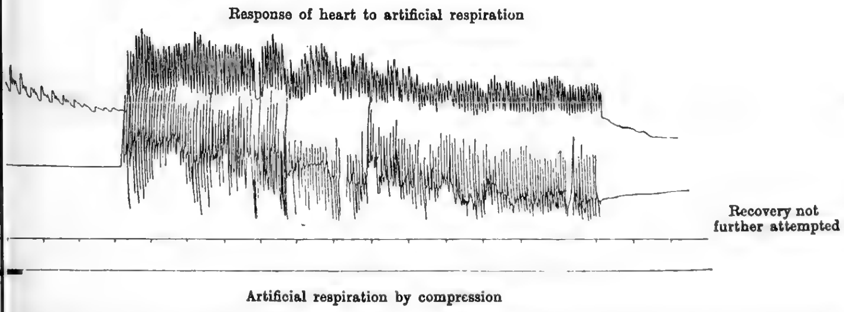
FIG. 10.—Dog: anæsthetized with chloroform. Tube in trachea. Both vagi exposed and threads
c.c. water absorbed. The blood-pressure tracing shows a slight initial rise, then a rapid fall due to car
height until cessation of respiration, when it gradually falls, although the heart continues to beat fo
During artificial respiration the heart responds to each compression of the thorax. (From the Procee



ıds in sea water, of which about 225 c.c. were aspirated into the air passages but 125 c.c. flowed out
recovery, first of the heart and afterwards of the respiration, although the latter continues irregular
vagus nerve. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)



ər, of which 430 c.c. were absorbed. Notice the quiet regularity of the respirations, which, however,
eat. Notice further the temporary resumption of respiratory movements after the heart has ceased.
ion. Eventually the inhibition becomes extreme. (From the Proceedings of the Royal Society of



sed round them but not tied. End of trachea tube submerged in water during three minutes; 160
inhibition. On now cutting both vagi the pressure rapidly rises and is maintained at a considerable
ırly two minutes. The respirations are slow throughout and cease after two and one-half minutes.
s of the Royal Society of Edinburgh, vol. xxv.)

was conceived that a large amount of air exchange might be obtained. Both this and the method of Marshall Hall were submitted in 1862 by the Royal Medical and Chirurgical Society to the investigations of a committee which made a number of experiments upon the cadaver. They apparently met with the same difficulties which their successors 30 years later found to be insuperable, and in most experiments they obtained no adequate amount of air exchange by either method; but such difference as there was appeared to be in favor of Silvester's method. As a result of their report, which was really quite inconclusive, the Silvester method was put in the first place by the Royal Humane Society and was adopted as an alternative method by the National Life Boat Institution. It was also taught, along with others, by the Royal Life Saving Society, when that Society was established in 1891, and it has now for many years been the method chiefly employed in Great Britain and in many parts of the Continent of Europe for resuscitation of drowned persons.

In the year 1869 there was published in New York the description of another method, depending not upon traction or posture but upon pressure alone, by Dr. B. Howard, under the title "Plain Rules for the Restoration of Persons Apparently Dead from Drowning." In these plain rules Dr. Howard first instructs you to turn the patient face downwards and press two or three times with all your weight upon the back so as to press the water out of lungs and stomach; then to turn the patient on his back and, kneeling over the lower part of the body, you are directed to grasp the patient's naked chest and squeeze his two sides together, pressing with all your weight; then with a push, suddenly jerk yourself back—repeating the operations eight or ten times a minute. This method differs from the Marshall Hall method not only in employing pressure as the main active agent in effecting air exchange, but also in the position of the body. In this respect the Howard method resembles the Silvester, the patient in both being laid on the back, with a roll of clothing under the shoulders. In the Marshall Hall method the position is never supine but is alter-

nately prone and lateral. This is a very important practical difference, especially in drowning cases. For in such cases there is apt to be a considerable accumulation of watery mucus, and in the supine posture with the head thrown back this will accumulate in the throat and obstruct the passage of air. An even greater disadvantage is the tendency of the limp and swollen tongue of the drowned subject to fall back into the fauces when in the supine position. In order to prevent this it is necessary to have an assistant to hold it and draw it forward out of the mouth—no easy matter under any circumstances without a special instrument. It is clear, therefore, that, even if efficient in producing air exchange, both the Silvester and the Howard methods are contraindicated in cases of drowning and in all other cases of asphyxia where there is an accumulation of mucus in the air passages, by reason of the obstruction produced by such accumulation; to say nothing of the obstruction caused by the falling backwards of the tongue. These objections do not apply to the Marshall Hall method, but on the other hand it is doubtful if the rolling of the patient on his side, which was looked upon by Marshall Hall as the essence of his method, adds greatly to its efficiency.

Having been baffled in our attempts to measure the relative amounts of air exchanged by these several methods in the cadaver, we proceeded to make experiments in a similar manner in the living subject. It is well known that if a number of deep respirations be made in succession it is easily possible to cease breathing for a short time and to remain entirely passive. We took advantage of this circumstance to test the amount of air which could be pumped in and out of the chest by each method, although with a thoroughly effective method this prior superaëration would not be required. We at first employed for the purpose of measurement a counterpoised glass bell-jar inverted into water and partially filled with air, and simply pumped air from the lungs through a mask or through a mouth tube (the nostrils being closed) in and out of the bell-jar. We found by this method that it was possible by any one of the methods ordinarily employed to pump in and out of the lungs

more than the amount of tidal air. But as we could not by this means make experiments over any length of time, a few inspirations and expirations of the same air being all that it was possible to produce in consequence of the rapid vitiation occurring in it, we adapted water valves to a spirometer, so arranged as to allow the atmospheric air to be drawn into the lungs and to direct the expired air into the spirometer. By this means with a large spirometer it was possible to continue

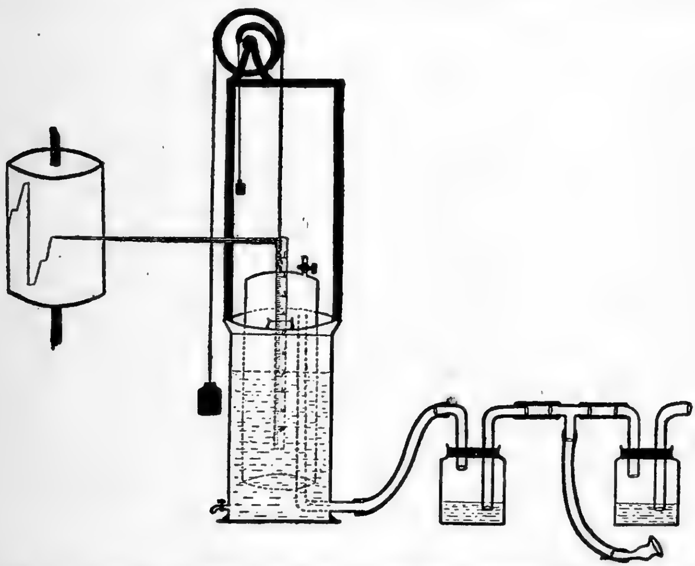


FIG. 11.—Diagram of method employed to measure the amount of air breathed per minute and per respiration. (See also Fig. 1.) (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.

the artificial pumping for some minutes and to determine the air taken in and given out not merely during a single movement, as had always previously been done, but to measure the amount during one, two, or five minutes, as might be desired, while the amount pumped at each single movement could be recorded by a pen attached to the spirometer and writing on a slowly moving cylinder (Fig. 11).

Experiments made in this way showed at once how difficult and well-nigh impossible it is to effect for any length of time

a sufficient exchange of air by the Silvester method. The most forcible pulling up of the arms, the body being held down by an assistant, produced a far less respiratory exchange than the tidal air of the individual under experiment. The amount was increased by alternating the traction with pressure on the chest; but even with this we were unable to maintain a normal exchange, and the subject began to feel suffocated and was compelled to breathe on his own account. The amount of exertion to the operator was, and is well known to be, extreme when the Silvester method is employed; in spite of this the method proved entirely inefficient when attempted for even a short period of time.

The Marshall Hall method gave a rather better exchange, but it was difficult to maintain it at a sufficient standard to obviate the *besoin de respirer;* and here again it was clear that the pressure part of the method greatly aided towards rendering it more efficient, the rolling of the subject being by itself inefficient.

The Howard method proved more effective. It is true that by this method the normal amount of respiration per minute was not always attained in our experiments; but it was not so markedly below normal as the other two and the deficit did not—at least within a short time—produce the same feeling of distress to the subject of the experiment, or evoke the same necessity to breathe, as with the other two methods.

Since the simple pressure method with the patient in the supine position gave results much superior to the traction method in that position, and since we had found that in the Marshall Hall method the pressure upon the back with the subject in the prone position greatly helps towards efficiency, we next proceeded to measure the amount of air which could be pumped through the lungs merely by pressure upon the back with the subject lying prone. After a few attempts we soon found that the best situation to apply pressure is over the lowest part of the back (loins), and that the amount which could be so exchanged per minute—pumping at the previously ascertained natural rate of respiration of the individual—was

FIG. 12.—To illustrate the prone pressure method of artificial respiration. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

not only greater than that yielded by any of the other methods, but could easily be brought up to or even beyond the natural amount respired. As a result of this the *besoin de respirer* was not present at all, and it was possible to continue the pumping action for apparently an almost unlimited time without the subject feeling the least desire to breathe naturally, the air exchange effected by this method of artificial respiration being entirely sufficient to maintain the normal gaseous exchanges.

This method, which I have called the *prone pressure method of artificial respiration,* is performed in the following manner: The subject, whether a drowned person or not, is allowed to lie prone, *i.e.,* face downwards, no preliminary manipulation of the tongue being required. The operator kneels or squats either across or on one side of the subject facing the head, and places his hands close together flat upon the back of the subject over the loins, the fingers extending over the lowest ribs. By now leaning forwards upon the hands, keeping the elbows extended, the weight of the operator's body is brought to bear upon the subject, and this not only compresses the lower part of the thorax but also the abdomen against the ground, the pressure being fairly equably distributed. The result of this is that not only is the thorax diminished in extent from before back, but, owing to the pressure which is communicated to the abdomen, the viscera are compressed and tend to force the diaphragm up, so that the thorax is diminished in capacity from above down. This is no doubt the reason why the pressure method when applied in the prone position is more effective than when applied, as by Howard, in the supine position. The pressure is applied not violently, but gradually, during about three seconds, and is then released by the operator swinging his body back, but without removing his hands. The elasticity of the chest and abdomen cause these to resume their original dimensions and air passes in through the trachea. After two seconds the process is again commenced and is continued in the same way, the operator swinging his body forwards and backwards once every five seconds or about twelve times

a minute, without any violent effort and with the least possible exertion. This last condition, viz., the absence of muscular exertion other than that involved in swinging forwards and backwards, renders it possible to continue the process without fatigue for an indefinite time. It can further be carried out unaided, by a woman almost as well as by a man, by children upon children; it hardly requires to be taught—a simple demonstration sufficiently teaches it to a large audience. Its advantages in drowning cases over any method which involves the supine position are sufficiently obvious—for with it there is no risk of obstruction by water or mucus or the contents of the stomach, which cannot accumulate in the throat but must come away by the mouth; and the tongue, in place of falling back, as in the supine position, falls forwards, and is unable to produce obstruction.

The Royal Life Saving Society has now decided to teach this method to the exclusion of any other. I have little doubt that this decision will result in the saving of many lives which would certainly be sacrificed by the employment of the comparatively complex methods hitherto practised. For these require special training and in some cases considerable muscular power to carry out, and some at least are of doubtful efficacy.

This prone pressure method, in common with pressure methods in general, depends for its efficacy upon the fact that after an ordinary expiration the lungs still contain a considerable amount of air which can be expelled by a forcible expiration. The volume of this, which is known as the *reserve* or *supplemental air*, is variously given; but the lowest determination (I quote from Pembrey) is 1148 c.c.; while the highest—that of Bostock—is 2624 c.c.[6] We may reckon it as averaging 1500 c.c., which is probably not an excessive estimate. It will clearly not be difficult to expel one-third of this amount by pressure upon the chest and abdomen; and this quantity would be considerably more than the average amount of tidal air, which, at a rate of respiration of 12 per minute, is, as we have seen, about 440 c.c. My own experience is that with a mobile well-developed chest it is easy to expel three-quarters of a litre

or even a litre. Of course on relaxing the pressure the same volume of air must pass in again, as the chest resumes its former shape and size. But it must be remembered that the opening of the glottis is not large and a certain time must be allowed for the passage in and out of air. Hence it follows that the movements will be more efficacious if they are not repeated too rapidly.

RELATIVE EFFICIENCY OF METHODS OF RESPIRATION.

Mode of respiration	Number per minute	Air exchange per respiration	Air exchange per minute
Natural	13	450 c.c.	5850 c.c.
Silvester	13	175 c.c.	2280 c.c.
Howard.............	13	310 c.c.	4030 c.c.
Marshall Hall........	13	254 c.c.	3300 c.c.
Prone pressure	13	520 c.c.	6760 c.c.

Statistics: Age of subject 23. Height 5 ft. 7¼ in. Chest at mammary line 38 in.
Weight 10 st. 1½ lbs. Vital capacity 4450 c.c.
Pressure exerted in performing respiration 60 lbs.

FIG. 13.—Table showing the relative efficiency of various methods of respiration.

The table which is here shown (Fig. 13) gives the results obtained in a series of experiments upon a single individual operated on by the various methods which I have described. In the first line the amount of air exchanged per minute and per respiration with natural respiration as well as the natural rate of respiration are indicated; the second line shows the amounts yielded by the employment of the Silvester method; the third by the Marshall Hall method; the fourth by the Howard or supine pressure method; and the fifth by the prone pressure method—the rate of artificial respiration being in all these cases about the same as the natural rate. The relative amounts have also been graphically recorded in the accompanying staircase tracings taken upon a slowly revolving drum; they show the extent of movement of the spirometer cylinder with each movement of artificial respiration. Each interval between the horizontal lines marked in the tracings represents 500 c.c. Each "rise" of the staircase marks the amount of air pumped out of the lung by the expiratory movement; at each "tread" air is being drawn into the lung by the inspiratory movement. This amount is pumped into the spirometer by

the succeeding expiratory movement, and so on until the upper limit of the blackened paper on the recording drum is reached. The spirometer cylinder is then lowered and a new staircase begun. The first of these tracings (Fig. 14) shows the amounts obtained in natural respiration; the second (Fig. 15) by the Silvester method; the third (Fig. 16) by the Howard method; and the fourth (Fig. 17) the amounts pumped by the prone pressure method. The time tracing at the bottom of each curve shows a mark every ten seconds.

I was much interested—after the results which I have just placed before you were published—to receive through my friend Sir James Russell, M.D., of Edinburgh, a memorandum from Dr. Henry B. Baker, Secretary of the State Board of Health, Michigan, which reads as follows:

"The article by E. A. Schäfer, on artificial respiration, reminds me of experiments by the late Prof. R. C. Kedzie and myself, about thirty years ago, at which time we concluded somewhat the same as Mr. Schäfer—that the prone position was best and that pressure over the lower ribs was important. We added another movement which I have thought useful; but, from Mr. Schäfer's results, it may not be necessary and it adds to the work. I refer to the lifting by the shoulders, shown in Fig. 2 on the leaflet I send herewith. The method has been successfully employed a few times on persons apparently drowned."

The figures from the leaflet and their description explain themselves. In the first, the patient is shown being raised bodily and jerked up and down two or three times with head down to get rid of water and mucus. In the second he is grasped by the clothing and the chest is raised from the ground. In the third he is replaced on the ground and pressure is made on the back over the lower ribs, long enough to count slowly one, two. The operator then suddenly lets go, grasps the shoulders, and raises the chest again; then presses on the ribs again—and so on.

That Professor Kedzie and Dr. Baker thoroughly comprehended what should be done and what should not be done is clear from their general instructions: "*Avoid delay. A moment may turn the scale for life or death.* Dry ground, shelter, warmth, stimulants, etc., are of secondary importance. The one

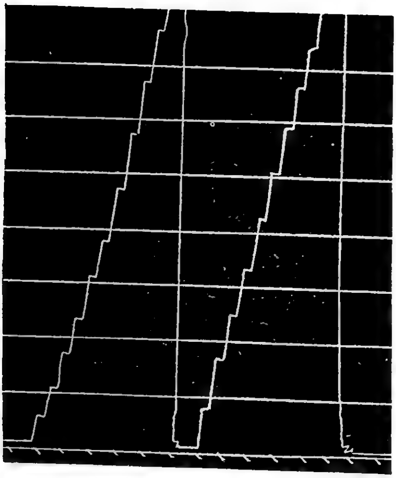


FIG. 14.—Results obtained by natural respiration, employing the method of registration shown in Fig. 11. The intervals between two successive horizontal lines represent half a litre (500 c.c). (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

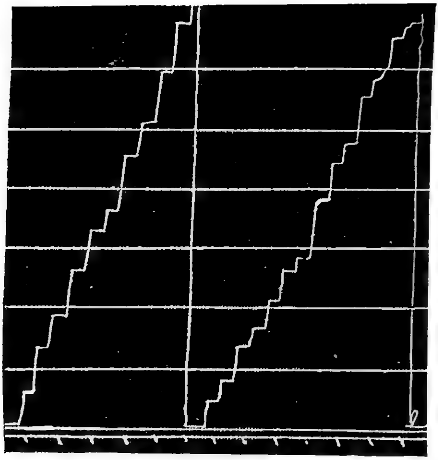


FIG. 15.—Results obtained by the Silvester method. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

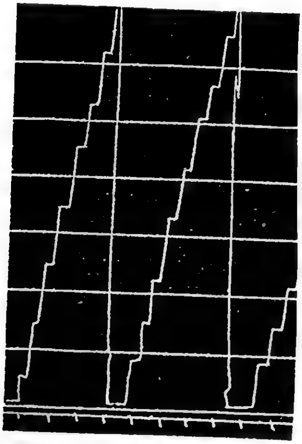


FIG. 16.—Results obtained by the Howard method. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

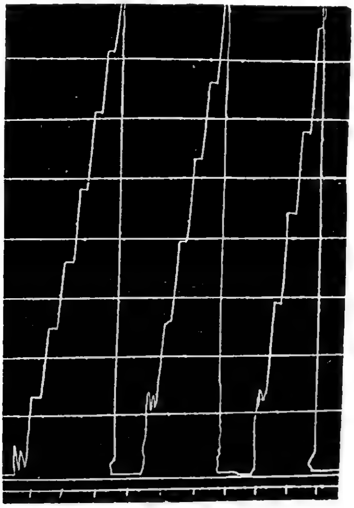


FIG. 17.—Results obtained by the prone pressure method. (From the Proceedings of the Royal Society of Edinburgh, vol. xxv.)

action of first importance is artificial breathing. *Do not stop to remove wet clothing.* Precious time is thereby wasted. . . . Before natural breathing is fully restored, do not let the patient lie on his back, unless some person holds the tongue forward. The tongue by falling back may close the windpipe and cause fatal choking.''

These general instructions can hardly be improved upon. The usual directions to remove clothing, to convey the patient to a dry warm place, to slap the face or body, to arrange the patient with a roll of clothing under the body and with the head lying upon the arm are only so many death traps. It is not even necessary or desirable to loosen the collar or waistband (which the leaflet I am quoting from recommends should be done) or the corset in women. Nothing should be attempted which will postpone the commencement of artificial respiration for a single instant. No fact emerges more clearly in the experiments which we carried out upon animals than the importance of immediate action.

The surgeon will naturally inquire concerning the value, and indeed the necessity, of the prone position for resuscitation of undrowned persons. Is it likely to prove of equal value with the supine position in cases where artificial respiration is required in the operating theatre? The answer to this question naturally depends upon circumstances. If the condition requiring artificial respiration shows itself before the operation has commenced, or if the operation is not on the ventral aspect of the trunk, the prone pressure method should be adopted. But if the operation has been commenced and is upon the front of the body—*e.g.*, an abdominal operation—it may not be possible to carry out artificial respiration in this position. In that case the Howard method may be employed. In drowned subjects this method is dangerous on account of the risk of producing rupture of the congested liver. But in other cases this risk does not exist; at least not to the same extent. And the method is more efficient and less laborious than that of Silvester. Theoretically Silvester's ought to be the best, but the limp muscles of the half-dead subject have very little effect in pull-

ing the ribs upwards. On the other hand, Howard's method must be applied cautiously in senile subjects with brittle ribs and ossified rib cartilages. When Dr. Howard came over to Europe he exhibited his method, amongst other places, at Dublin. The Rev. Dr. Samuel Haughton (whose name was well-known in those days in connection with the muscular mechanisms of the body, although it is not now often seen in text-books) volunteered to be the subject of the demonstration, and Dr. Haughton being no longer young, and Dr. Howard displaying considerable energy, the experiment resulted in the fracture of some of Dr. Haughton's ribs.*

In passing, I may mention a simple method of performing artificial respiration which is efficient in most individuals, but which, unlike the methods I have been describing, requires apparatus although of but a simple character. I may here interpolate that before Marshall Hall's method was introduced, several others had been described, all involving the employment of apparatus of greater or less complexity, which, of course, was never at hand when the drowned person was fished out of water. There is therefore little cause for surprise that these methods were seldom or never used. But the one of which I am speaking only demands the employment of a pair of domestic bellows. Many years ago Horwath showed that by placing the nozzle of a bellows in one nostril—the other may be left open, but the mouth should be closed—it is possible by suddenly compressing the bellows to inflate the lungs to a considerable extent, and, by repeating this inflation rhythmically, respiration can be maintained. Unfortunately even this simple piece of apparatus is usually not available in those places where drowning is liable to occur. And I have my doubts whether domestic bellows are any longer to be found generally in England—where in my younger days almost every room was provided with a pair—although they are met with in most parts of America, where wood is still extensively used as fuel. In surgical cases the bellows method might usefully be employed, and in operations involving the opening of both pleuræ such a

* This incident has been narrated to me by an eye-witness.

mode of performing artificial respiration would even be necessary. But in these cases it would probably be safest to perform tracheotomy, and to blow up the lungs through a tube inserted into the windpipe, allowing escape of the expired air by a lateral aperture, much in the same way as artificial respiration is ordinarily carried out in animals in physiological experiments.

Finally I do not hesitate to say that by reason of (1) its relative efficiency, (2) the ease with which it is carried out, even by a single operator, (3) the absence of risk of injuring the liver or fracturing the ribs, (4) the facilities afforded for the escape of fluid from the mouth, and (5) the natural tendency of the tongue to fall forward, the prone pressure method is the one which commends itself for general adoption in most cases that require artificial respiration, and above all in cases of drowning.

REFERENCES.

[1] Hutchinson: Article, Thorax, Todd's Cyclopædia of Anatomy and Physiology, vol. iv.
[2] Marcet: Proc. Physiol. Soc., Journ. Physiol., xxi, 1897.
[3] Borelli: De Motu Animalium; quoted along with several other references here given from Pembrey's article, The Chemistry of Respiration, in Schäfer's Text-Book of Physiology.
[4] Jurin: Phil. Trans., xxx, 1717–19.
[5] Vierordt: Physiol. d. Athmens, Karlsruhe, 1845.
[6] Pembrey: Article, The Chemistry of Respiration, see above.

THE RÔLE OF FERMENT REVERSIONS IN METABOLISM *

ALONZO ENGLEBERT TAYLOR, M.D.,
Professor of Pathology, University of California, San Francisco.

THE biologic sciences are rarely able to avail themselves of the use of theory, as can so commonly be done in the physical sciences, in such a way that the theory serves as a prophecy for the future, as well as an articulation with the past. When, however, phases of biologic knowledge are securely founded on a physical basis, it becomes possible to review a subject from the point of view of theoretic interpretation. Within recent years such a procedure has become possible in several directions in physiology.

The subject of the rôle of ferment reversions in metabolism is naturally one of great interest; and, as the barristers say of a line of interrogation in the introduction of evidence, the proper foundation has been laid for it. It must be clearly realized, however, that if such a procedure as I contemplate is to be made profitable, the scope of inquiry must be extended to the broadest limits of biologic matters. The inquiry may be made under three general headings:

1. What is the status of the theory of reversion of chemical and physical reactions in the pure sciences?

2. What are the specific facts tending to demonstrate that the theory holds in the concrete sense in biologic material?

3. What are the facts in physiology, as yet more or less devoid of reasonable explanation, that may be logically classed as instances of such reversions, and grouped as such under a comprehensive theoretic interpretation?

Finally, it will be interesting to contrast the physiologic with the physical station of equilibrium.

---

* Lecture delivered April 18, 1908.

The types of reaction concerned in the reversion within biologic bodies are varied. Many of them are anhydrations, condensations, reactions in which water is added to form larger molecules; such are the reactions concerned in the synthesis of carbohydrates, fats, and proteins. Others are reductions and oxidations. Very important from the constructive point of view are the intramolecular rearrangements. Of this class there are two groups, depending on whether the mass of the molecules is invariable or varied. An illustration of intramolecular rearrangement without alteration in molecular mass, strictly isomeric, is to be noted in the sugars. Within the body the three hexoses, *d*-glucose, *d*-gelactose, and *d*-levulose, are subject to conversion into one another. That the different hexoses tend thus to pass into the isomeric sugars as a chemical reaction was shown years ago by Lobry de Bruyn and Van Ekenstein. These reactions, as will be pointed out, are of very widespread occurrence in the vegetable kingdom. Illustrations of intramolecular rearrangements, which are of the greatest importance, including alterations in the molecular mass, are to be found in the different forms of protein reactions.

The term "ferment reversion" constitutes a verbal incongruity. The reactions under consideration are, of course, not inaugurated by the presence or the action of the ferments; the enzymes simply accelerate the velocity of already progressing reactions. The autoreactions that are accelerated by enzymes are, in themselves, the expressions of the reaction qualities of the substance involved and progress to an equilibrium in accordance with the laws of mass action and equilibrium. There are no energy relations, but solely the relations of reaction velocity, concerned in the process. By clearly realizing this fact it is possible to avoid the absurd blunder into which many medical writers fall, namely, that the theory of the reversion of ferment reactions constitutes a violation of the law of the conservation of energy. The additional objection, frequently stated with pronounced apprehension, that the theory of synthesis by reversion of reaction involves a restriction of the scope of the so-called vital activities of the cells, must unqualifiedly be admitted

to be based on fact. This, however, in my humble opinion, is no loss to either biology or chemistry.

The first heading that I have given does not require long consideration. It is not necessary to-day to elucidate the theory of the reversion of chemical reaction. No proposition in theoretic chemistry is more firmly established; and modern treatises practically rest on the flat dictum that all chemical reactions are reversible, if the proper conditions are attained. In the domain of physics the facts are not always so clear. While some of the most exquisite illustrations of reversion are noted in physical reactions (as, for example, in the two forms of crystallization of sulphur), the notion is current that colloidal reactions are not reversible. A great deal of hasty and immature work has been done on the subject of the colloids; and of no other subject of experimental investigation can it be so emphatically stated to-day that the experimental data lead to conflicting and incongruous inferences. It is clear, however, that included within the so-called colloidal reactions are at least two factors: purely chemical reactions and the reactions of capillarity, using the term in the strict sense of Willard Gibbs. Now a review of the theory of capillarity does not support the notion that the colloidal reactions are not reversible; that is a purely arbitrary assumption, and is not included in the mathematical formulation of the theory of capillarity. So far as the purposes of this article are concerned, however, this whole matter is quite immaterial; for we shall be concerned almost exclusively with purely chemical reactions. For our purposes, therefore, unlimited use may be made of the physicochemical theory that all reactions are reversible and tend to stations of equilibrium, in which the opposing reaction progressions are compensated and balanced. In direct analogy to the kinetic theory of gases, we must believe that in chemical systems there is no cessation of reaction, but only the exact counterbalancing of unceasing opposing reaction progressions.

The demonstration of the occurrence in biologic systems of the reversions that were predicated by theory followed closely on the definite establishment of the theory in the mother science.

The experiments *in vitro* have, in many directions, demonstrated such reactions and have attracted widespread attention, because the accomplished reaction constitutes a synthesis. Ten years ago Croft Hill synthesized isomaltose from *d*-glucose under the action of a vegetable maltose. Since this time isolactose has been synthesized by Fischer and Armstrong; and isosaccharose by Wroblewski; while such artificial sugars as tri-acetyl-glucose have been synthesized through ferment action by Acree and Hinkins. That in all the instances of the synthesis of disaccharides the isomer has been obtained in no wise affects the validity of the result. In the hydrolysis of maltose, lactose, and saccharose the iso-sugar appears as the first product of the reaction. Whether the analytical results in the reported experiments are due to the time factor, the experiments not having been allowed to continue long enough to permit the final product to be found, or whether the stereo-isomeric relations have been the determinants in the outcome, cannot now be stated. The synthesis of glucosides, so closely related to the disaccharides in general conformation, has also been accomplished by Fischer. The definite synthesis of a definite polysaccharide has not yet been accomplished. The reported results of the synthesis of glycogen by Cremer, and of starch by Wolff, Fernbach, and Maquenne, have not been properly established by indisputable analytical demonstrations. These same reversions may be accomplished with inorganic catalysors, as was shown years before the investigations with the ferments, when Wohl and Fischer synthesized isomaltose from glucose, under the action of sulphuric acid. The fact that when the synthesis is accomplished under the action of sulphuric acid, the iso-sugar is formed, as is the case with the ferment reversions, robs this fact of any specific significance.

The synthesis of a monosaccharide, like glucose, from a product of its fermentation, has not been accomplished, nor even rationally attempted. Between *d*-glucose and its products of fermentation, ethyl alcohol and carbon dioxide, there are at least two known intermediary stages: methyl glyoxal and lactic acid. The formation of the first stage, lactic acid, from

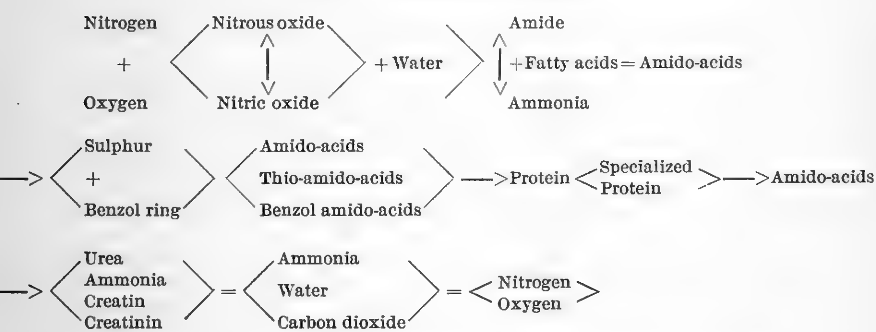
ethyl alcohol and carbon dioxide, could not be accomplished except under very high pressure of the carbon dioxide in the system; in the analogous synthesis of sulphuric acid from zinc sulphate and gaseous hydrogen, eighteen atmospheric pressures of the hydrogen were found necessary. The report by Albertson of the synthesis of *d*-glucose from ethyl alcohol and carbon dioxide under the action of zymase, was not only lacking in analytical foundation, but was devoid of the necessary theoretical basis.

The synthesis of fats through ferment action was easily accomplished. Almost simultaneously Berninzone and Kastle and Loevenhart synthesized lower esters of the normal series, as did later Hanriot. Later still Pottevin and Taylor were able to form the normal higher fats, using respectively, the lipase from the pancreas and the castor bean. The structural relations are here very clear. The composition of the products is easily capable of absolute demonstration. Artificial esters can also be found, and apparently the condensation of an alcohol and a fatty acid represents the most feasible illustration of a reversed ferment action. It must not be forgotten, however, that the autoreaction proceeds here with a demonstrable velocity; so that the condition is one extremely favorable to the demonstration of catalytic or enzymic acceleration. The formation of these fats may also be easily accomplished under the influence of inorganic catalysors.

The synthesis of proteins from amido-acids through the action of ferments has not been accomplished with the ease noted in experiments with the fats and sugars. The investigations of Fischer in the condensation of amido-acids to the so-called peptides indicate that the conditions for the reaction not only are difficult to secure, but must be rigidly maintained. In a word, the synthesis of protein in the laboratory will be much more difficult than was the synthesis of sugar. Years ago a long series of negative investigations was published by Taylor, and Abderhalden has likewise published the details of negative experiments. A year ago I reported the synthesis of protamin, the simple protein occurring in the spermatozoa of fishes,

from its component amido-acids, through the action of a trypsin obtained from the livers of a California clam. As the substrate of this experiment, I employed the digested products of protamin. Though the positive results observed in the experiments with the trypsin were not observed in the controls, nevertheless, the experiment lacked the complete validity that could be obtained were the reaction accomplished from the pure amido-acid. This experiment I have since repeated, and I am able to state that by bovine trypsin and by trypsin from the clam, protamin may be synthesized from arginin and the monamido-acids contained in protamin, isolated and purified by the Fischer ester method.

Chart 1.—Nitrogen Metabolism.



This leads up to the main subject of inquiry: What are the facts in metabolism that may be logically grouped under a theoretic interpretation resting on the proposition of reaction reversion? Let us examine, first, the protein metabolism. Chart 1 illustrates the chain of facts in the nitrogen-metabolism in biology.

The formation of the oxides of nitrogen from the gaseous oxygen and nitrogen of the atmosphere is a function fundamental to the lower forms of plant life, and probably also of animal life. That these oxides are formed in the air by electrochemical reactions is, of course, certain; but it is equally certain that the reaction, as related to bacterial life, is entirely independent

of this, and probably exceeds it largely in quantity. Between the two oxides of nitrogen an equilibrium exists. All bacterial cultures that produce the one produce the other. All bacteria that form nitrite from nitrate also form nitrate from nitrite. Mammalian juices have the same properties.

The next step lies in a combination of water with the oxides of nitrogen, with the production, through reduction, of amide and ammonia. The direct combination of nitrogen with hydrogen apparently does not occur. The nitrogen is first oxidized and then reduced. These reductions are also the functions of lower vegetable and animal life. Apparently here, also, an equilibrium exists; though, in the attempt to manufacture ammonia from nitric oxide, it has been difficult of definition. Culture experiments on the action of bacteria upon the cyanamides, however, indicate clearly that the reactions are reversible.

The next link in the chain consists in the combination of the amide with fatty acids to form amido-acids. The derivation of the fatty acids will be considered later. This reaction marks a great rise in biologic dignity, and is resident in all the higher plants. While some of the invertebrate forms of animal life are able to subsist on ammonia and amides, the higher forms cannot accomplish the synthesis of amido-acids from the fatty acids. The reaction is typically and regularly reversible in vegetable life, as may be seen in the germination of seeds. Plants produce, further, two particular groups of amido-acids, those containing sulphur and those containing benzol. These compounds, indispensable to animal life, cannot be formed at all in the higher animal organisms. Man, for example, cannot form amido-thio-acids from sulphur in whatever form he ingests the latter; he cannot ingest benzol and from it form benzol-amido-acids; for these two special compounds he is absolutely dependent on the plant world.

The final step in the anabolism of nitrogen lies in the condensation of the several amido-acids to proteins. This reaction, most difficult *in vitro,* as the studies of the Fischer school indicate, is apparently accomplished by all plants and animals. While one must not be dogmatic on this point, the experimental

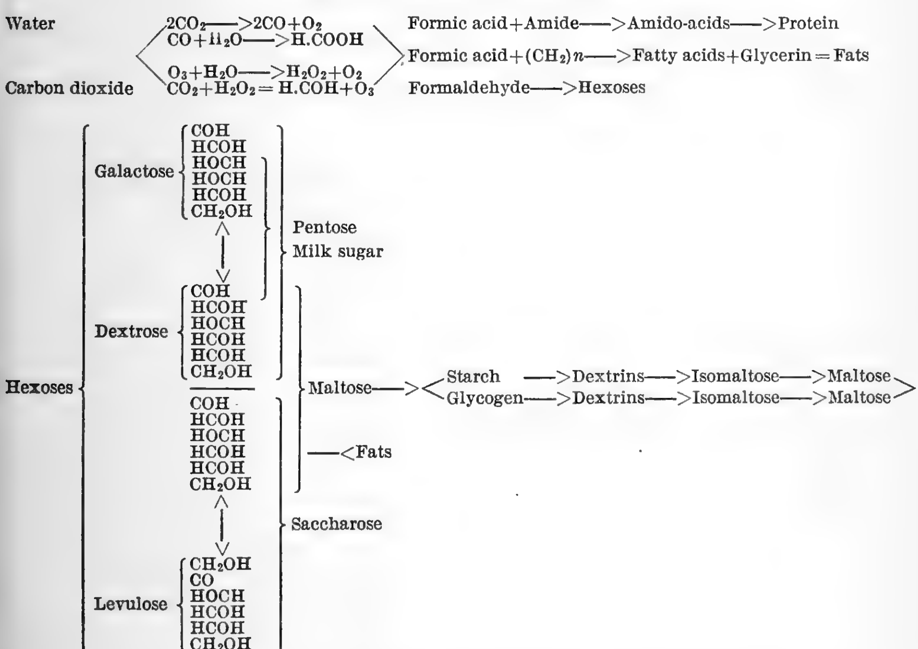
investigations indicate that in the dog and the rabbit the nitrogen metabolism may be supported by amido-acids; that is, the organism is able to form protein from the amido-acids. From the common protein, typified by serum albumin, the organism forms the specialized body proteins, myosin, reticulin, hæmoglobin, casein, etc., by intramolecular rearrangement of the amido-acid groups. This completes the chain of synthesis. Under the influence of intracellular ferments, the proteins of the body are hydrolyzed to the component amido-acids, and these are then subjected to desamidation, cleavage, and further oxidation, the nitrogenous moiety appearing as urea, ammonia, and the members of the creatin group. These reactions are common in type in all classes of animal and plant organisms. By the action of bacteria the end-products of higher organisms are reduced to gaseous nitrogen, oxygen, and water, thus completing the cycle. The two chief differences between the chemical activities of mammals and those of the lower plants lie, on the one hand, in the fact that our organism cannot complete the cycle; on the other hand, in the fact that in man the specialization of proteins reaches a much higher stage. What has been lost in adaptation has been compensated by specialization in synthesis. Man has learned to apply the lesson in this to the world below him; the nitrobacteria are made to serve the higher plants, just as these plants serve the higher animals.

The entire cycle constitutes a reversion in the physical sense. In the chemical sense, it can be shown that nearly all the individual stages or reactions are capable of reversion in the organism in which they occur. The digestion of proteins is an act of hydrolysis, the proteins being split into their component amido-acids. In this form they are largely, if not entirely, absorbed. While it may be admitted that the products of digestion above the stage of the several amido-acids are, to some extent, capable of resorption, we realize that the velocity of resorption must be a function of the diffusibility of the substance; and, therefore, in the quantitative sense, the principal resorption is unquestionably that of the amido-acids. In the portal vein, the material is to be found largely in the form of

common protein. Where has this condensation occurred? Obviously in the intestinal wall. How? The only available and logical interpretation is to predicate a reversion there, under the influence of enzymes. It is, however, not a qualitative reversion; for the particular proteins that were in the diet are not to be found in the blood; only serum albumin and the globulins are there. Which of these is first formed is not definitely known; but general considerations lead to the inference that it is the serum albumin that is primarily formed from the products of the digestion of protein, and that from it the serum globulins are formed. The serum albumin presents no biologic stamp; the serum globulins possess specific biologic properties, which we infer were bestowed on them in the conversion from serum albumin. In all probability there is a relation of equilibrium between these several blood proteins; in any event, the two globulins are known to polymerize in either direction, and the same fact probably holds for serum albumin and soluble globulin. These blood proteins are the substrate from which all the specialized proteins are formed. These syntheses are concerned entirely with the groupings of amido-acids, in both the qualitative and the quantitive sense. In general it may be said that the different specialized proteins contain the same amido-acids, but in different amounts, and inferentially in different intramolecular relations. But, in addition thereto, some proteins contain certain amido-acids that are not found in others. Thus some proteins are rich in glycocoll, tyrosin, or thio-amido-lactic acid, while others contain little of these, and a few, indeed, none at all. The researches of the Fischer school have given us our first insight into these intramolecular arrangements. and we may expect much additional light on this subject during the next few years. The reactions of the protein catabolism resemble, in all their chemical details, the tryptic digestion of protein. There is every reason to believe that the autolytic cellular degenerations are carried to the stage of the amido-acids. From these the creatin, creatinin, urea, and ammonia are derived, and represent in general terms the end-products of the nitrogenous metabolism. To what extent

these are correlated in functional, as well as in chemical derivation, is not yet clear. There exists good evidence tending to separate the creatin from the urea metabolism. On the other hand, there is no doubt that creatin and creatinin may be converted into urea, just as may uric acid. That the variables in creatin, creatinin, urea, and ammonia might represent the rela-

Chart 2.—Carbohydrate Metabolism.



tions in an equilibrium-system seems to have been overlooked by workers in this subject. The body juices are able to form urea from ammonia and ammonium carbonate, and ammonia from urea. The equilibrium in this reaction was long ago established by Fawsitt. The body forms urea from amido-acids, but, as far as is known, the reversion of this reaction does not occur in the body. These lower reactions, below the stages of the amido-acids, are not performed by the digestive juices, and

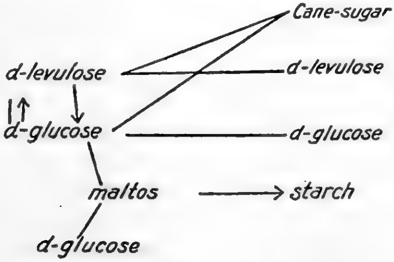
in this respect autolysis differs from tryptic digestion. We deal here, of course, with two superimposed enzymic reactions. The fact that urea can be formed *in vitro* from arginin, from monamido-acids, and from different ammonia salts, by animal extracts, removes the entire subject of urea formation from the domain of cellular physiology, in the older and commonly accepted sense of that term.

The cycle for the carbohydrate metabolism is shown in the second chart.

The reactions given for the first stages in the reduction of carbon dioxide are drawn from two sources: bacterial investigations and chemical studies on the silent electric discharge. That chlorophyl, in the presence of sunlight, reduces carbon dioxide is, of course, a fact long known. Recent investigations have shown that ozone, hydrogen peroxide, and formaldehyde are formed; and the reactions given in the chart represent the most simple and logical way of stating these facts. Loeb's investigations, corroborating the earlier work of Warburg, have shown that the same substances are formed when carbon dioxide is reduced in the electrochemical reaction. When it is recalled that Fischer has synthesized the sugars from formaldehyde, the scheme becomes very impressive. From the formic acid we may naturally predicate the derivation of the various fatty acids, which, combined as amido-acids, are the component of proteins. From formic acid, also, we may, by direct progression in synthesis, rise to the higher fatty acids that form, with glycerin, the natural fat. There can be no doubt that the fats are formed from sugar, and both routes are indicated in the chart.

The reactions up to the stage of the six-carbon sugars occur in all plants and apparently in some of the lowest forms of animal life—unless we cling to the old classification by which chlorophyl absolutely distinguishes plants from animals. Whether the sugars are formed by regular progression, the hexose from the pentose, is not known, but it is unlikely; while it now seems certain that in the higher animals glucose can be formed from pentose, and *vice versa,* it is certain that in plants the hexoses are not formed through the stage of pentose.

Once the stage of the hexose is attained in plants, most interesting reactions occur. From general evidence it may be assumed that *d*-glucose and *d*-levulose, respectively, aldehyde and ketone sugars, are the primary hexoses. These, as first shown by Lobry de Bruyn and Van Ekenstein, undergo intramolecular rearrangement into each other. Many plants contain *d*-galactose, in the state of glucoside; and this is, in all probability, derived from *d*-glucose by intramolecular rearrangement. The relations of equilibrium between *d*-glucose and *d*-levulose are varying in different plants and under different conditions. The situation of this equilibrium is complicated by the fact that the two sugars are also undergoing combination to form cane sugar. In the sugar-beet and in the sugar-cane equal amounts of the two hexoses are formed, and the combination is quite complete, so that the juices of these plants contain largely cane sugar. In many other plants, the quantities of the two hexoses vary, and the amount combined into the disaccharide varies. Thus, some berries yield largely *d*-levulose, others *d*-glucose and little cane sugar, while other berries contain more *d*-glucose and much more cane sugar. Some dates present a large amount of cane sugar; others contain *d*-glucose largely, with less of cane sugar and not a little of uncombined *d*-levulose. In such plants as form starch, the relations become still more complex, since maltose is being formed from the *d*-glucose, and from this, in turn, starch. Thus:



Any consideration of equilibrium must needs, therefore, be concerned with five states in a chemical system containing primarily two chemical substances. More than this, the relations

vary with time. In the unripe banana, starch is present in predominating amount; as the fruit ripens, *d*-glucose and *d*-levulose appear more and more. These combine; so that when fully ripe there is much cane sugar present. Over-ripe bananas display a marked inversion of their cane sugar, due, not to bacteria, but to post-mortem digestion. It is common in fruits and plants to find the reactions largely in one direction, as to the stage of starch, during the period of growth; while during the period of ripening these reactions are reversed, and the products return to the state of sugar. In the case of the grains and seeds, on the other hand, the carbohydrates remain during the period of ripening, and the reversions occur during the period of germination; but throughout the scene reversions dominate the situation. In another group of plants, reversions occur between fats and sugar. Thus, in the cocoanut, fat is formed from the sugar during the period of growth; while during the period of ripening sugar is formed from fat. Some of the plant diseases act through such reversions. Thus, there is a disease of the sugar cane in which the reversion leads to an excess of primary sugars. There is another disease in which an abnormal polymerization to a dextrin occurs. Both are unquestionably fermentative.

Passing now to the relations in higher animals, similar conditions are encountered. On digestion, starch is hydrolyzed to maltose, and this then to glucose. Maltose can be reabsorbed, as it is readily diffusible; but, since it appears in the blood only as *d*-glucose, it must have been inverted during its passage through the walls of the digestive tract. Milk sugar and cane sugar are also split into their component hexoses during the act of digestion. They also, being diffusible substances, can be reabsorbed; but just as in the case of maltose only *d*-glucose appears in the blood, so that they must have been inverted during their passage through the wall of the digestive tract. This inversion function of the mucosa of the alimentary tract has been too often overlooked and constitutes an indispensable factor in the digestion of carbohydrates. Maltose can be hydrolyzed to some extent in the blood and tissues, but apparently

cane sugar and milk sugar cannot be inverted within the tissues, and are eliminated unchanged.

The only glucose to be found in the blood, no matter what the diet, is *d*-glucose. Therefore, during the act of resorption through the alimentary tract, *d*-levulose and *d*-galactose, components respectively of milk sugar and cane sugar, are converted by intramolecular rearrangement into *d*-glucose; again, without doubt, the reactions of fermentation. These reactions can occur also in the tissues and fluids of the body to some extent. When *d*-levulose is ingested it is largely utilized; *d*-galactose, to a much less extent. That the body does not burn *d*-levulose and *d*-galactose cannot be stated or proved; but it is much more likely that the body first converts them into *d*-glucose. In a similar manner it cannot be denied that the bacteria of glucose fermentation act on them; but it is much more likely that they are first converted into *d*-glucose and then fermented.

The *d*-glucose is, therefore, the common body sugar, the substrate of the carbohydrate metabolism. From it the body forms glycogen, just as plants form starch; and just as the starch is stored until, during the period of its maturation or germination, it is reconverted into sugar, so the glycogen is stored until, the body having drawn on its mass of sugar, it suffers inversion. Without doubt the mass of sugar is the essential factor; there is a station of equilibrium between sugar and glycogen. When the sugar is augmented by ingestion the reaction proceeds in the direction of glycogen. When the mass of sugar is reduced by combustion the reversed action occurs. Fat is also formed from sugar; and here, too, some such relation of equilibrium must hold, though the situation is not at all clear.

The conversion of *d*-levulose into *d*-glucose, which occurs in the mucosa in the alimentary tract, is not reversible in the animal body. The conversion of *d*-galactose to *d*-glucose, on the contrary, is reversible, and the reversion constitutes two important physiologic processes. Integral to the central nervous system are combinations of *d*-galactose with lipoids; the *d*-galactose is formed in the body, because the growth of the nervous

system is not dependent on the presence of *d*-galactose in the diet, and the blood contains only *d*-glucose. This (*d*-glucose) is also carried to the active mammary gland, there in part converted into *d*-galactose, and combined with an equal mass of *d*-glucose to form milk sugar. If this lactose be then resorbed from the mammary gland into the circulation it cannot be utilized or split and is eliminated unchanged.

This brief summary will indicate that in animals, as well as in plants, the carbohydrate metabolism presents a large number of facts that can be reasonably interpreted only on the theory of reversions applied to fermentative processes.

Coming now to the catabolism of the carbohydrate metabolism, we may assume that *d*-glucose is the single substrate of the reactions of carbohydrate combustion within the body. That section of the chart devoted to this portion of the cycle is an

CHART 3.—CARBOHYDRATE CATABOLISM.

$$\text{Glucose} \longrightarrow \text{Methyl glyoxal} \longrightarrow \text{Lactic acid} < \begin{matrix} \text{Ethyl alcohol} \\ \text{Carbon dioxide} \end{matrix}$$

adaptation of the scheme of Stoklasa and Bach. It contains the possibly startling assumption that the combustion of sugar in the body passes through the stage of ethyl alcohol.

The scheme is not capable of direct proof to-day. It is based on the following groups of facts: Known bacterial combustions follow the scheme; reactions *in vitro* with ferments follow the scheme; reactions *in vitro* with different methods of oxidation follow the scheme quite closely; it presents no chemical difficulties; and, lastly, nearly all the substances denominated are known to occur in the normal body, and those not definitely known to occur are such as are with great difficulty determinable—for instance, the aldehyde. It cannot be compared directly with the scheme for the anabolism of carbohydrates, as there is there a breach between the stage of formaldehyde and that of sugar.

Of this scheme, the only part that concerns us in a discussion of ferment reversion is that above the stage of lactic acid. For reasons before mentioned, a combination of ethyl alcohol and

carbon dioxide could not be expected to occur in the body. The reversion from lactic acid to *d*-glucose can be easily made *in vitro;* and your president, Graham Lusk, has advanced good evidence that it occurs in the body.

Despite the apparent simplicity of the chemical composition of the fats, the steps in their natural synthesis are not clearly understood. Unquestionably, they are first formed in vegetable life by up-building from the lower fatty acids. When fatty acids are formed in the laboratory, one observes an undoubted tendency for them to be formed in series of even carbons. The higher fats occurring in nature belong largely to the even-carbon series; and the assumption is, therefore, natural, that two $(CH)_2$ groups are added in each step. The formation of the higher fats from carbon and water is the function of all plants, unless we are to assume that in plants the synthesis of the fats may be, instead, *via* the route of sugar. That in many plants, particularly in seeds and fruits, the reversed reaction, sugar <——> fat—fat <——> sugar, is a prominent reaction, is well known. Whether the higher animals form fats from the lower fatty acids is not definitely known. If we knew whether, in the formation of fat from sugar, the sugars were first built down to lower fatty acids, we should know from what point in the scale of the fatty acids the animal organism is able to synthesize the higher fats; but the steps in the conversion of sugar into fat in the animal organism are entirely unknown. The synthesis of glycerin is easily accomplished in both plants and animals. The power of the animal organism to modify higher fats seems to be extremely limited, and this is expressed in the familiar experience that the fats of the diet are deposited in the body unchanged. On the contrary, when the body forms fat from carbohydrate, the species of the animal concerned is of determinate importance. Cattle, horses, dogs, and swine will form from the same carbohydrate fats containing very different relative amounts of palmatin, stearin, and triolein. If, however, these four animals are fed fats, these will be deposited unchanged in the tissues. We may formulate this in the terms of the law that body-fat, when derived from in-

gested fat, is specific to the diet, when formed from carbohydrate, specific to the species.

In the digestion of fats we deal with a simple cleavage. I think it may be stated to-day, without fear of contradiction, that fats are absorbed only after cleavage into glycerin and fatty acids, and not in the form of an emulsion. In the fluids of the retroperitoneal lacteal circulation the fats are found again recombined. This recombination of the fatty acids and the glycerin must have occurred during the process of resorption through the intestinal mucosa—clearly an act of direct and simple reversion. Following this occurs a very important condition, which has been generally overlooked. The fat of the body is present in two forms: first, as insoluble neutral fat, represented by the fatty depots of the body; and second, in a soluble state in the circulating fluids, the fat in this instance being in combination with some other unknown component and the combination constituting a soluble and diffusible substance. This fact, first described by Connstein, I have been able to verify. It indicates, probably, the following situation:

Depot fat is storage fat purely, is not susceptible to any reaction, and corresponds, in the fatty metabolism, to what glycogen is in the carbohydrate metabolism. The active chemical state of fat in the metabolism is the form which is in soluble, diffusible combination. This is the active mass, in the reaction sense, in the fat-metabolism. Between these two conditions an equilibrium must exist. When there is a heavy combustion of fat, reserve fat is transferred to the soluble state; when there is a diminished combustion of fat, soluble fat is transferred to the reserve state.

The combustion of fats within the body is not well understood. Probably in plants fats are never burned, but if utilized are always first reconverted into sugar. For the animal organism, recent chemical work by Dr. Dakin—work of great importance, not only to the physiologist, but likewise to the pathologist—has indicated that when fats are burned they are built down in regular sequences of the even series. That is, stearin is built down to palmatin, etc.; and this condition occurs

down to the stage of butyric acid. Unquestionably, the end products of the fat combustion must be here, again, acetic or formic acid. A decision as to whether the combustion of fats beyond butyric acid passes through the stage of beta-oxybutyric acid, is not essential to the present argument, and the question cannot be here discussed. However accomplished, whenever a $(CH)_2$ group is split off and carbon dioxide and water formed, the reaction cannot be reversed under ordinary conditions, except under pressure of carbon dioxide. In plants the entire series of reactions may be regarded as reversible; in animals, on the contrary, the scope of the reversions is comparatively narrow. In the animal body, fat is formed from sugar. Whether this reaction is reversible, and whether in the animal body sugar is formed from fat (as asserted by Pflüger), cannot now be decided. There can be no question that the view of Pflüger is very attractive; it offers a simple, natural and logical explanation for some of the most difficult situations in chemico-physiology, and is supported by the analogy in the vegetable kingdom. It is, however, devoid of any direct demonstration.

In the purin metabolism we deal with what chemically is probably the most complicated of the functions of the body. Nuclein contains, as you will recall, a pyramidin body, purin bodies, pentose, and phosphoric acid. It is firmly established that the body needs none of these in the diet, except, of course, phosphoric acid. The egg contains, practically speaking, no purin, pyramidin, or pentose; but the embryo contains in its nuclei large amounts. Obviously, therefore, the growing organism is able to synthesize all these; and to the great biologic importance of this synthesis the recent researches of Jacques Loeb have given emphasis. Chemically, it is certain that pyramidin and purin may both be formed from amido-acids, so that the substance for their derivation is abundantly present in the proteins of the body. Pentose is undoubtedly formed from glucose—a reaction that may be easily accomplished in the laboratory. These are then combined by reduction and anhydration, to form nucleinic acids, which enter into combination with protein. When nuclein is ingested it is split, in the act of

digestion, into its component groups. In all probability these are never utilized in the synthesis of the body nuclein. In a word, the animal organism is not only independent of ingested nuclein from animal or vegetable food, but is probably unable to utilize purin, pyramidin, and pentose furnished to it through the alimentary tract. Exogenous purins and pyramidin and pentose are either burned or eliminated *in toto*. In other words, the digestive reaction of cleavage of nuclein is not reversible in the body. The synthesis apparently follows other lines. On the death of the cell the nuclein contained in its component parts is split, and the pentose, purin, and pyramidin are eliminated or burned. In other words, the waste products of nuclein metabolism are, like the products of nuclein digestion, of no further utilization in the body. In this metabolism, therefore, we have apparently no illustrations of a direct reversion in the animal body. In the larger sense, however, we have one illustration of such a reversion. The ripe egg of fishes, as first shown by Meischer, contains no nuclein. The unripe egg, however, does contain nuclein in its protoplasm. On hatching, the embryo, of course, contains nuclein. With the ripening of the egg there is a disappearance of the nuclein; with the germination of the egg, a reappearance of the nuclein —and all within the same minute organism. Here, therefore, we have an illustration of a reversion in the purin metabolism. In the matured animal organism, however, we have none.

These general remarks illustrate clearly, I believe, the fact that reversions constitute some of the most important and indispensable chemical reactions occurring in animals, as well as in plants. A few points only require further elucidation.

To what shall we attribute the reversions? To ferments, undoubtedly. To what ferments? There is a growing unfortunate tendency in biologic literature toward a multiplication of the ferments. For this the terminologic practices of the Ehrlich school are in part, no doubt, responsible. As you are aware, when Ehrlich encounters a difficulty he is inclined to invoke a new force to explain it. Thus early in the investigations on diphtheria poison he assumed in diphtheria toxin the

presence of but two or three substances, in order to explain all the apparent experimental facts. As the experimental facts have increased, this number has been amplified, until now more than a dozen hypothetical substances are assumed to be necessary to explain the facts. If this doctrine were applied to the ferments we should soon have an uncountable number of ferments, each acting in an infinitely small capacity. We know, for example, that in many of these reactions there are many intermediary stages. If we are to assume a specific ferment for each stage, we shall soon be in hopeless confusion. For example, between glucose and alcohol, we have certainly methyl glyoxal and lactic acid, and probably one other stage. According to this use of the concept "ferment" we might assume four ferments to be necessary for alcoholic fermentation. Now, considering the general chemical principles that (1) in a series of reaction progressions the first stage produced is not to the final, but to the least stable, stage, and so on until the final stage is reached; and (2) that this series of intermediary reactions in no wise affects the chemical conception of reaction as related to the mass of the primary reacting bodies; it is clear that this tendency to the multiplication of ferments must be resisted, if clarity is to prevail. Platinum black can form alcohol from sugar; and there is no reason why zymase should not do it just as well. A more serious blunder is being made in the assumption that in the reversions other ferments are concerned, that one ferment forms sugar from glycogen, and a different ferment forms glycogen from sugar. Now to the physiochemist, this is a complete nullification of the argument. If a ferment cannot work in both directions, it cannot work in one direction. The ferment simply accelerates the velocity of the reaction that is progressing toward the station of equilibrium, irrespective of the direction in which the station of equilibrium lies. The lubrication of the bearings of a locomotive reduces the friction, and, therefore, increases the speed of the locomotive, irrespective of whether it is going forward or backward. The assumption that ferments can work in only one or the other direction involves a complete collapse of the theory

of catalytic acceleration of reaction, and is absolutely untenable according to the modern conceptions of the physical and chemical sciences.

Lastly, one extremely interesting theoretical consideration remains: the mechanism by which the conditions of reversion are accomplished. Nitrogen and oxygen will not combine in air, except in infinitesimal quantities, because of the low temperature. As the temperature is raised, the station of equilibrium is shifted in the direction of the oxides of nitrogen. When, as occurs to-day in the commercial manufacture of these oxides, an arc-discharge is passed through a current of air, with the production of these oxides, we are dealing with a thermochemical reaction. At the high temperature produced in the discharge of the arc, nitrogen and oxygen combine; the station of equilibrium is shifted in their favor, and the velocity of combination is increased. Unless these oxides are promptly combined, before cooling occurs, dissociation will take place. In the formation of the oxides of nitrogen in plants and bacteria, on the other hand, no such temperature factor can be invoked. Here some other factor intervenes to shift the station of equilibrium. What is this factor? We do not know.

A somewhat analogous consideration holds in the reduction of carbon dioxide. Chlorophyl, in the presence of sunlight, is able to reduce carbon dioxide to formaldehyde—a reaction that does not occur in appreciable amount at ordinary temperature, in the presence of either chlorophyl or sunlight alone, when carbon dioxide and water are in contact. Here we are dealing with a photochemic reaction, the effect of which is again to shift the station of equilibrium in the direction of the product of combination. The same thing occurs in the silent electrical discharge, as illustrated in the equations of Walter Loeb—unquestionably here, however, not photochemic in nature. In plants the formation of stereo-isomeric sugars must be associated in some way with the presence of circumpolarized rays in our solar light. Theoretically, in the reversion of such reactions, the stereo-isomeric influence must be a factor. These considerations apply, of course, to the physiology of all organ-

isms, animal and plant. Undoubtedly, the reduction of carbon dioxide and the formation of the sugars are photochemic reactions purely, whether they occur in plants or in animals. The formation of the oxides of nitrogen, on the other hand, and of the building-stones of protein, is not photochemic, nor is it thermochemic. A few years ago Engelmann published a calculation designed to show that at the instant of chemical combustion within the cell extremely high temperatures are developed. Even granting the entire argument, however, I do not believe that this fact could be utilized to explain the association of nitrogen and oxygen in the bodies of bacteria.

In the reversions that are known in higher organisms, what constitute the general conditions? According to the laws of general chemistry, the conditions determining the station of equilibrium are the temperature, the concentration of the total system, and the mass of the reacting bodies. These are, in part, operative, of course, and can be used to explain many of the phenomena. When sugar is burned by violent exertion the mass of sugar in the body becomes reduced, and, of course, the reversion-reaction, glycogen to sugar, becomes stimulated. There are, however, reversions in which these will not hold. We are not able, by the variation of the known chemical factors, to determine the stations of equilibrium as they are observed in physiology. In the purely chemical system the mass of the catalysor is not a determining factor; in the ferment systems, however, it is a determining factor. The station of equilibrium depends on the temperature, the total concentration of the system, the masses of the reacting bodies and their products, and the mass of the ferment. We are able *in vitro* to show an influence on the station of equilibrium due to the mass of the ferment. We are not able *in vitro,* however, even with this factor, to explain the remarkable reversions that occur within the body; nor are we able to account for the velocity of the reversions. The body accomplishes in a few hours what the most painstaking experiments will not accomplish in weeks. There are apparently present in the living body, but not yet attained in our experiments, conditions involving the station

of equilibrium and the velocity of the reaction that determine the marked difference between the results of nature and those of the laboratory. That these as yet unknown factors are purely chemical or physical must, of course, be believed. While, therefore, we know of the rôle of reversions in the body, that is, that such and such reactions constitute reversion and occur in the body, what we do not fully appreciate or understand is the velocity with which the reactions that can be accomplished without, as well as within the body, occur within it.